

H.M. Meyer

**DEPARTMENTS OF LABOR AND HEALTH, EDUCATION,
AND WELFARE APPROPRIATIONS FOR 1964**

HEARINGS
BEFORE A
SUBCOMMITTEE OF THE
COMMITTEE ON APPROPRIATIONS
HOUSE OF REPRESENTATIVES
EIGHTY-EIGHTH CONGRESS
FIRST SESSION

SUBCOMMITTEE ON DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND
WELFARE AND RELATED AGENCIES APPROPRIATIONS

JOHN E. FOGARTY, Rhode Island, *Chairman*

WINFIELD K. DENTON, Indiana

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ROBERT M. MOYER, *Staff Assistant to Subcommittee*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Part 3

National Institutes of Health

Printed for the use of the Committee on Appropriations



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DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1964

THURSDAY, MARCH 7, 1963.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. STUART M. SESSOMS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS, NATIONAL INSTITUTES OF HEALTH

RICHARD L. SEGGER, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Mr. FOGARTY. The committee will come to order.

We have before us this afternoon Dr. Shannon, the Director of the National Institutes of Health.

GENERAL STATEMENT

Doctor, you have a 29-page statement. Do you want to put that in the record, and give us a summary of it?

Dr. SHANNON. Yes, sir.

(The statement follows:)

Mr. Chairman, and members of the committee, I am grateful for this opportunity to appear before you again and assess broadly the progress and needs of the National Institutes of Health. Before I speak of our programs directly, however, I should like to relate them to the Nation's total investment for research and development. While official estimates are not yet available, it seems reasonable to assume that the Nation's total investment in research and development in 1964 will be in the \$18 to \$20 billion range. The President's budget estimates that Federal expenditures for this purpose will reach \$14.9 billion, about \$13.3 of which will be devoted to the areas of national security, space exploration, and atomic energy. These expenditures so vital to our national interest are largely applied to the development of hardware—space vehicles, missiles, nuclear reactors.

The medical research dollar is an investment in human well-being—in the improvement of the health of our people, in the conquest of the conditions and diseases that harass mankind, physically, socially, economically. Thus, a major share of the medical-research dollar is invested in the advance of fundamental knowledge, rather than the application of known principles. Moreover, this

knowledge is directed in the broadest sense toward improvement in the well-being of man—his health, behavior, and ultimately his economic and social condition.

Over the past 5 years, Federal expenditures for medical and health-related research have nearly kept pace with Federal expenditures for all research (minus development), which have more than quadrupled—rising from approximately \$1 billion in 1958 to an estimated \$4.5 billion in 1963. NIH funds continue to comprise a significant segment, remaining at about 14 percent of the total. I wish to say, with a deep sense of appreciation, that this much-needed expansion has been due in no small measure to the interest, the wisdom, and the efforts of this committee.

Today NIH is the largest contributor to the country's medical research, providing nearly 40 percent of the total funds and helping substantially to sustain the research and research training programs of educational institutions. At the same time, the overall growth of medical research is in line with the general development of science and technology in the Nation.

Mr. Chairman, if I may digress for a moment, I should like to indulge in heresy. There is a substantial basis to justify support for research as an end in itself—as enabling scientists to pursue their ceaseless quest for new knowledge, the ultimate result of which must be a gain for all. Support for medical research, however, has gained extensive acceptance because it is a means to a clearly understandable end—improvement in the well-being of our people, conquest of the diseases that shorten our lives and scourge us with misery and suffering. It is these basic humanitarian considerations that have always been uppermost in my mind as I describe the programs and objectives of NIH.

On the other hand, I think it is important to emphasize that the fruits of medical research do, in fact, contribute substantially to the Nation's economic growth in many ways. It is, of course, extremely difficult to gage precisely the full economic impact of medical research activities supported by the National Institutes of Health and all other sources. Nevertheless, I believe it reasonable to advance the concept that medical research expenditures do exert a considerable general benefit in terms of their ultimate effects upon:

1. Labor force, by increasing the numbers available, by reducing the death rate, extending productive years of life, and diminishing disability.
2. Productivity and personal income, by adding specialized skills through training programs, by reducing disability and time lost due to illness, and by improving control over nondisabling but efficiency-reducing conditions.
3. The gross national product, through expanded output made possible by a larger and more productive labor force and through investment in long-term growth producers such as education and the advancement of knowledge.
4. Taxes, by increasing revenues and achieving more effective public expenditures for health services and medical care, and by diminishing the burdens of institutionalized populations.

Mr. Chairman, I believe this glimpse of the economic context of NIH activities is a fitting introduction to my statement, since it reflects broad responsibilities to the fields of science and medicine inherent in our programs—responsibilities which I shall again ask your committee to help us meet. I refer to the importance of sustaining and guiding medical research in this country at a level consistent with the national economy, the research opportunity, the dimensions of the health problem itself, and the substantial contribution that medical research can make to economic growth. Again the results of these hearings will affect the magnitude and direction of the Nation's medical science in an important way.

The budget being presented for NIH operating programs totals \$930,554,000. This represents an increase of \$112.9 million, or approximately 14 percent, over the comparable 1963 operating level. Looking more closely at the requested increase, it should be noted that more than 40 percent is earmarked for the mental health area in response to compelling national needs pointed out in the President's message on mental illness and mental retardation. As we review the details of this budget, I believe you will agree that it constitutes a sound plan for moving ahead in the national attack upon the major diseases of man. As a preface to the discussion of specific plans for 1964, however, it seems necessary to deal quite frankly with some broad issues related to the general level and effectiveness of the NIH programs. As you know, Mr. Chairman, a number of voices have raised questions about the scope and magnitude of Federal research activities, particularly medical research. It is time, I feel, to step back and take a realistic look at the present circumstances and the criticisms being made.

These points are clear:

First, the Nation, through public and private agencies, has called for and supported in recent years a major assault on disease and conditions adverse to health, as part of a broad national effort to improve human welfare.

Second, enormous progress has been made in the development of knowledge which is fundamental to this movement. Later, I will touch on recent highlights of this progress, and our program directors will report in detail upon advances in their fields.

Third, we have reached a stage in medical science where it can be clearly seen that we face the most complex problems ever presented to the intelligence of man. This stage is analogous to that which confronted the field of physics at the beginning of World War II, when it was apparent that only an extraordinary application of resources—funds, facilities, and manpower—would enable science to attain the tremendous goals in sight. To achieve the scientific capabilities requisite to the tasks envisioned meant enormous investment in heavy equipment—cyclotrons, atomic reactors, complex instrumentation, and in large scale, complex scientific organizations. We have come to accept these aspects of the physical-science development. In a like manner, we must realize that biomedical research is approaching a similar state, where substantial investment in resources, facilities, and coordinated efforts is essential to create the environment for major advances, to secure the capability to capitalize quickly upon emerging opportunities, and to translate new knowledge into effective development and utilization.

Let us look specifically at some of the more promising and urgent areas. Research into the cause of cancer is one. Here, we have exciting leads, particularly in relation to the role of viruses. A large-scale coordinated approach involving many aspects of scientific activity seems essential to the free exploitation of current possibilities. Another such field, largely concerned with carcinogenesis, is the toxicology of trace compounds found in the environment—particularly the question of their metabolism and possible cumulative effects. This is a field of vital importance which requires massive effort along basic lines. In these and many other areas, we have reached the stage where research opportunity will place extraordinary demands on the resources available.

One approach to health problems which offers enormous potential, but calls for expenditure on a new order of magnitude, is the study of large numbers of people in pursuing clues to the causation of disease. Through modern advanced computing equipment, it is possible to assess systematically the phenomena surrounding the emergence of disease in whole population groups, in a manner which will yield leads not detectable in laboratory or clinical observation. Another development is the enormous progress being made in clinical investigation, in the study of both normal and pathological life processes in a scientifically monitored and controlled clinical setting involving large complex instruments and specialized services. The opportunities are at hand and the state of the art sufficiently advanced to assure progress in these areas. But we must face the fact that increasingly medical research will require major efforts, involving a high degree of coordination, expensive facilities and resources, and skilled manpower.

I repeat, Mr. Chairman, the prospects are bright. Throughout the scientific community, there is a sense of excitement and a conviction that we stand on the brink of substantial advances. Consequently, I feel no reluctance or misgiving in presenting a budget at this level or in setting forth the dimension of our proposed effort in fiscal 1964. Although it may seem large in terms of the past, the NIH budget represents a small portion of the total Federal investment in research and development. I believe it is commensurate with the problems before us, the research opportunities, the circumstances of present scientific activity, and the expectations of the entire world.

During the past year a number of organizational and administrative changes were made in NIH programs with a view to more efficient discharge of our broad categorical missions. These changes reflect new scientific perspectives and new managerial policies.

I should like at this time to introduce Dr. Stuart M. Sessoms, who has succeeded Dr. David Price as Deputy Director of NIH. Dr. Sessoms joined the NIH staff in 1953. He served as Assistant Director of the Clinical Center and as Associate Director of the National Cancer Institute with responsibility for the cancer chemotherapy program. In his new capacity as Deputy Director, Dr.

Sessoms is giving special attention to the policies and mechanisms of our research support programs.

Among the major organizational changes of 1962 was the authorization of two new Institutes under the provisions of Public Law 87-838, bringing to nine the number of Institutes composing NIH. One of these is the National Institute of Child Health and Human Development. This represents the creation of a broad new research program to investigate human health and development from prenatal life to senescence. I will return to this program later, but I should like to mention the appointment of Dr. Robert A. Aldrich as Director of this new Institute. Dr. Aldrich, a leading authority in the field of child health and former chairman of the Pediatrics Department, University of Washington, has just joined our staff.

Another change under Public Law 87-838 has been the promotion to institute status of the Division of General Medical Sciences and its programs of research and training in the sciences basic to health, and the appointment of Dr. Clinton C. Powell as Director. May I present Dr. Powell, former Assistant Director of our National Institute of Allergy and Infectious Diseases.

One other change that I should like to mention at this point is the creation by administrative action of the Division of Research Facilities and Resources in July 1962. Dr. Frederick L. Stone [indicating], former head of our Division of General Medical Sciences and other NIH support programs, is Chief of the new DRFR.

RESEARCH ACCOMPLISHMENTS

Returning now to the basic substance of NIH programs—the generation of new knowledge relating to health and disease—I am pleased to report to the committee, Mr. Chairman, that the past year has been especially fruitful, both at our own laboratories and Clinical Center at Bethesda and under our research grants. We are beginning to reap the rewards of expanded fundamental investigations in such important fields as cancer causation and treatment, mental retardation, diabetes, and certain stubborn infectious diseases of global significance. In the course of these hearings, many research advances in these and other areas will be described by the individual program directors, so I shall only mention a few highlights. These will not necessarily represent the year's most notable achievements, but will illustrate, I believe, the areas of emerging opportunity that are receiving intensive stimulation and attack.

Two lines of research in cancer, for instance, have held sufficient promise to warrant the creation of special task forces, which will mobilize resources and stimulate investigative effort. The first of these groups is concerned with leukemia therapy, the second with viruses as possible causes of human cancer. You will want to pursue these topics with Dr. Kenneth Endicott when he presents the budget for the National Cancer Institute.

In the field of cardiovascular disease, which Dr. Ralph Knutti will discuss, I should like only to mention our continuing progress in the study of blood pressure lowering drugs. We have previously reported to this committee on our clinical studies of a new drug, alpha-methyl DOPA, developed by Merck Sharpe & Dohme. Our experience indicates that this compound is useful both in malignant and less rapidly advancing types of hypertension. You will be interested to hear that alpha-methyl DOPA, already sold commercially in England, was recently placed on the market in this country.

Dr. Robert Felix will discuss important accomplishments in the mental health field, one of which concerns a grantee's discovery that a declining IQ in children preceded their development of schizophrenia. Another development in Dr. Felix's area is the launching of a 5-year program against phenylketonuria, or PKU, one of the known causes of mental retardation. The program will demonstrate the detection and dietary treatment, which have advanced to a point where control of the disease seems practical. I might add, Mr. Chairman, that basic research of the type which led to the understanding of PKU seems our best hope today of progress against the vast problem of mental retardation—a problem of multiple and complex causes, calling for a methodical, diversified, and very fundamental attack.

You may wish to ask Dr. Donald Whedon to discuss a rapid, sensitive method developed at the Arthritis and Metabolic Diseases Institute for detecting narcotics and other drugs in the urine. Other notable advances in metabolic diseases concern the possible detection of latent diabetes through new techniques.

Mr. Chairman, I should like to mention one more finding—an example of work in infectious diseases that seems particularly exciting. NIH investigators have been testing an experimental Parke-Davis drug against malaria in prison volunteers, and it can now be reported that a single injection has protected the volunteers for a year against infection from repeated challenge. Dr. Justin Andrews, Director of the Allergy and Infectious Diseases Institute, is prepared to discuss this further.

As an addendum to this review of accomplishments, Mr. Chairman, I should like to name a few NIH scientists who were honored during the past year.

The Joseph P. Kennedy, Jr. Foundation honored Dr. J. H. Tjio, of the National Institute of Arthritis and Metabolic Diseases, for his discovery of the exact number of chromosomes in man—a contribution of particular significance to the field of mental retardation.

Dr. Thelma B. Dunn, of the National Cancer Institute, received the Distinguished Service Award of DHEW, the Federal Woman's Award, and an honorary degree from Woman's Medical College of Pennsylvania. Dr. Dunn is an internationally acknowledged authority on the pathology of cancer in mice.

Dr. Robert W. Berliner, of the National Heart Institute, also received the Department's Distinguished Service Award. He was honored for major contributions to knowledge of the kidney as well as outstanding direction of a major research program.

Dr. Wilhelm C. Hueper, for his renowned work on environmental causes of cancer, won the United Nations Prize for Cancer Research.

Dr. Joseph E. Smadel, of the Division of Biologics Standards, received the Albert Lasker Clinical Research Award for research on typhoid fever and scrub typhus, and an honorary doctor of science degree from the University of Maryland.

Recently, Dr. Marshal Nirenberg, of the Heart Institute, received the annual award of the Washington Academy of Sciences for increasing our understanding of the natural chemistry of protein synthesis.

MAJOR PROGRAM DEVELOPMENTS

In the interest of maximum progress in the future, and maximum efficiency in achieving it, certain major administrative changes which I have mentioned were carried out last year. I should like now to describe these for the committee in a little more detail.

Two new institutes

Mr. Chairman, the event of the past year that will assuredly have the greatest impact on NIH programs for years to come was the authorization by the 87th Congress of two additional Institutes. With the Secretary's approval, the Surgeon General established on January 30 of this year the Institute of Child Health and Human Development and raised to institute status our Division of General Medical Sciences.

These two Institutes are exceptional in being organized around a concept other than research on diseases categorically grouped. I want to emphasize, however, that their creation signals no change in previous NIH role or emphasis: our first order of business remains the improvement of national health through conquest of important health problems. The new Institutes represent a longer look, and a better organized attack, on basic aspects of disease and human development.

The National Institute of General Medical Sciences will carry on the important programs begun under DGMS which support training and investigations in the sciences basic to health. I hardly need emphasize to this committee the value of these programs in developing the scientists, in formulating the problems, and in providing leadership and support—all essential elements in research on problems of health and disease which are outside the categorical areas.

The National Institute of Child Health and Human Development is undertaking new programs and a new approach, but these are addressed to the same problems as the categorical Institutes. NICHD provides a new point of perspective from which health needs may be viewed. Its prime task will be to increase knowledge through identification, interrelation, and integration of health needs over the full life cycle. Specific responsibilities assigned to NICHD at the time of its authorization include "research and training in the special health problems and requirements of mothers and children and in the basic sciences relating to the processes of human growth and development, including prenatal

development." We believe that this new approach to the study of health and disease will prove efficient and productive.

Appropriate to its assignment, NICHD will have primary responsibility within NIH for implementing recommendations of the President's Panel on Mental Retardation. We are proposing that NICHD set up and administer a program of broadly based interdisciplinary centers for research in human development, which would spearhead the research attack on mental retardation as well as on other problems of the developmental process.

The Institute's needs for 1964, as well as those of the Institute of General Medical Sciences, will be discussed when the committee takes up their appropriations.

Division of research facilities and resources

The new Division of Research Facilities and Resources administers three programs transferred to it from the Division of General Medical Sciences. These are general clinical research centers, special research resource centers, and general research support grants. In addition, the Division administers the health research facilities construction program transferred from the Division of Research Grants and the primate centers program from the National Heart Institute.

It will be seen, Mr. Chairman, that the new Division consolidates the administration of some of the most important NIH programs for advancing the Nation's resources for research and developing the research programs of institutions. These programs are designed to strengthen the research environment in a planned and systematic fashion. They provide support for the framework of physical facilities and other resources that underpin productive research activity in the biomedical sciences. Last year, the committee asked for a progress report and a long-range plan for the Division. These have been completed and Dr. Stone is prepared to discuss them in greater detail.

All members of this committee, I believe, are acquainted with our general clinical research program, now in its fourth year. By the end of fiscal 1963, we expect that grants will have been made for about 70 centers throughout the country. We are now concluding the first phase of this effort. Our support has engendered the development of centers of clinical research capability across the Nation, particularly in areas where they are most needed. There is still further need, however, and we are requesting funds for the support of six new centers in fiscal 1964. Then, I believe we can expect a period in which these units can be brought to full and effective utilization in the advancement of clinical research. Further plans for the program will emerge from careful assessment of their activities during that phase.

In this connection, I should also like to mention briefly the categorical clinical research centers established through support by the several institutes. As you are aware, Mr. Chairman, we have had less success with these centers than with the general type, and are still trying to assess their true role. It is possible that the categorical needs could best be served by an organization comparable with a broad-spectrum research hospital, where the specialized requirements of investigators can be met under conditions primarily designed to give maximum assurance of the patient's welfare. Notwithstanding possible refinements, the categorical centers have been productive, and we are requesting substantially the same level of funds for their support as we did last year. This will permit a further evaluation of their role while continuing to meet special needs in the study of major diseases.

Mr. Chairman, I will discuss the activities of the Division of Research Facilities and Resources in greater detail when the committee takes up the "General research and services" appropriation.

Manpower and training needs

This brings us to the key resource for biomedical research—the trained investigator and his supporting technical staff. Before proceeding, however, I should like to announce to this committee that Dr. Charles V. Kidd, who has held several top posts at NIH, was recently appointed Associate Director for Training. This appointment reflects our determination to strengthen still further our ability to meet vital national needs for research manpower.

The 1964 budget is in continued support of that objective. We are requesting a total of \$218 million for training grant and fellowship programs, representing an increase of \$32 million (or 17 percent) over 1963 levels.

Of the increase, Mr. Chairman, about 60 percent (\$19.3 million) is directed toward a new thrust in the training of mental health personnel; about 15 percent (\$4.7 million) toward increasing allowances to institutions in connection with NIH fellowship awards, in line with Government-wide policy; and about 25 percent (\$8.2 million) toward further efforts to meet the Nation's medical research manpower needs as determined in our study made a year ago at your request. You will recall the proposition that we must aim at doubling the trained workers in medical and health-related research by 1970. This means an average annual addition of approximately 5,000 scientists to the manpower pool.

In terms of specific NIH programs, I should like to speak to those designed to provide predoctoral training, special training of clinical investigators, and career awards—all emphasized in special reports to the Congress last year. Our request takes into account the increased costs of training in these areas.

Training at the predoctoral level is designed to add to the available number of Ph. D.'s for research in the biomedical sciences. The program is expected to encourage talent at an earlier stage than has hitherto been possible. I should like to point out that the President's programs to develop physicists, mathematicians, and engineers will surely increase the competition for personnel. On the other hand, legislation proposed by the administration and now before the Congress would tend to enlarge the total pool from which all fields must draw by surmounting the economic barrier which at present denies higher educational opportunities to many talented young people. Our proposed 1964 training programs would supplement the administration's bill in providing requisite basic science manpower.

In postdoctoral training, there is a general need to develop medical investigators through the further training of M.D.'s and Ph. D.'s, particularly through combinations of medical and basic science backgrounds. More particularly, there is need for investigators trained in special fields, such as neurophysiology, epidemiology, and molecular genetics. We can no longer look to the individuals trained solely as M.D.'s for adequate numbers of competent clinical research scientists, and must approach this need through combined M.D.-Ph. D. training. The 1964 budget would enable the schools to proceed in that direction. NIH programs for postdoctoral training include graduate training grants for which a 17-percent increase is requested and postdoctoral and special fellowships, increased in about the same proportion.

Finally, I should like to mention here our new career award programs, which are designed, as you know, to provide long-term support for senior investigators. Two types of award are made—the Research Career Development Award and, for the highly experienced scientist, the Research Career Award. The former type, providing relative flexibility of program, represents the larger request—844 awards totaling \$13.5 million. The latter type, the Research Career Award, is the capstone of our training effort. The requested \$5.9 million would lend to the career stability of 286 outstanding scientists. We are requesting for both levels of career development a total of \$19.4 million to cover 1,130 awards including prior commitments.

Management of scientific and technical information

Among other administrative developments, Mr. Chairman, NIH has taken steps to intensify and formalize its traditional concern with the flow of meaningful scientific and technical information. The expansion of scientific programs in recent years has greatly increased the attention being given to the problem of information exchange, storage, and retrieval among members of the biomedical community and health practitioners; and undeniably a major research program such as ours has important responsibilities in this area. I have established a focal point for scientific and technical communications within my own office. In like manner each of the institutes and divisions is establishing a counterpart at a high level within its respective organization. This will provide the basic framework for our efforts. In addition, the Division of Research Facilities and Resources has been given broad responsibility for considering the support of biomedical communications services in carefully selected bioscience areas at appropriate institutions throughout the country. In short, we are moving ahead on a broad front in this difficult and complex field.

FURTHER IMPROVEMENT IN THE ADMINISTRATION OF GRANT FUNDS

During the course of the hearings last year, Mr. Chairman, I reported to the committee on the general nature of the efforts being made by NIH to improve the administration of our grant programs with a view to assuring the most effective furtherance of the public interest in the use of these funds. I emphasized at that time the growth of the support of medical research in this Nation through NIH programs had brought into being many complex and unprecedented problems in the relationship of the Federal Government to non-Federal institutions. As I have said earlier, funds made available through NIH research grants now constitute the major source of support for the medical research activities of this country. It is my conviction that these programs, representing as they do a unique joining of public and private effort, have fostered a highly productive era in the advancement of the health sciences.

The accomplishment of this great scientific effort has posed extraordinarily difficult administrative problems. These relate to changes in the magnitude and character of NIH activities and the obligations involved in the expenditure of large sums of public moneys. The essence of these problems has been to develop a set of terms and conditions governing the relationship between a Federal agency and the universities and research institutions in such a way as to maintain a wise balance between the obligations of public stewardship and the necessary conditions of freedom for the investigators involved. Such conditions are the essential basis of scientific creativity and productivity.

During the past year we have undertaken a series of major steps in further effort to strengthen the management of our grant programs. We have prepared a full report on these actions which we will be glad to submit to the committee in order that it may be fully informed of the nature of our efforts in this area. One of the more significant accomplishments in this respect has been the development and issuance of a manual to guide institutions and investigators receiving NIH research and training grants in the use of the funds thus made available to them. This manual sets forth the essential policies, terms, and conditions governing the relationship of the NIH as a granting agency to its grantees. I should like to quote from the preface of this manual because these words, I believe, set forth the basic concepts which underlie the various measures we have taken to strengthen our grant management activities. This quotation, I believe, will convey to the committee the basic objectives which we have sought through these changes:

"* * * While this manual is generally comprehensive, the full measure of responsibility which it imposes upon a grantee institution and upon individuals is broader and more fundamental than these specific terms.

"Under the terms of the grant, the institution and individual concerned enter into a very special relationship with the Public Health Service for the utilization of grant funds. This special relationship results from the basic nature of the grant as a conditional gift in response to a request for support of a venture in which there is a substantial measure of public interest.

"A grant, therefore, represents a mutual joining of interests on the part of the grantor and the grantee institution in the pursuit of a common objective. In this relationship the grantee assumes with the granting agency the obligation to act in the public interest in achieving the common purpose. This is a relationship of trust which imposes upon the grantee the responsibility—

"1. To assure that the grant funds are utilized for the purpose for which they were given.

"2. To exercise the same probity and prudence in their expenditure that is extended to the use of the grantee institution's own funds.

"It is to these broad obligations that a recipient of a Public Health Service grant is accountable. This manual does not attempt to specify the full extent of the considerations which should bear upon a grantee in the use of grant funds.

"There is, however, an area of appropriate concern for the Public Health Service in assessing the adequacy of the administrative practices and mechanisms employed by the grantee to assure, in general, the conditions of prudence and, specifically, conformity with the terms of this manual.

"An examination by Public Health staff of the administrative processes, controls, and mechanisms utilized in the expenditure of grant funds will be part of the continuing overview of Public Health Service grant programs in the further administration of these programs."

As you can see from the words of this preface, it is our view that an effective accomplishment of the objectives of our programs involves heavy reliance on the responsibility of institutions who are recipients of grant funds to utilize these moneys with prudence and in full recognition of the public purpose for which they have been made available. We believe that one of the essential tasks confronting us in administering our programs under these concepts is to assure that grantee institutions are, indeed, able to discharge the obligations which they assume for administering grant funds. In this respect the recent increase in the allowance for indirect costs to 20 percent, authorized by this committee for the current year, and the President's proposal incorporated in our current budget presentation to allow a further increase in allowances for indirect costs, will provide substantial assistance in strengthening institutional capability in grants administration.

Mr. Chairman, I believe we are making significant progress in adjusting our administrative practices and framework to the requirements involved in being accountable for sizable sums of money. I am very pleased to report this progress to the committee. I should be less than frank, however, if I did not emphasize my continuing concern with the overwhelming necessity of avoiding, in our efforts to tighten administration, actions which may seriously contravene the essential conditions of scientific productivity. Maintaining a wise balance between the necessary exercise of accountability on the one hand and the conditions essential to excellence and productivity in research on the other presents profound and far-reaching problems.

I must emphasize again that, in my view, the key to reducing those problems lies in providing a set of terms and conditions governing the grant relationship which assures the maximum exercise of responsibility upon the part of the recipient institutions and investigators, rather than centrally determining and specifying in ever-greater detail the manner in which the funds made available can be expended. If the Federal Government is to achieve its essential purposes in the health sciences, we must find a way to accept, without detailed specifications and rigidity, a basic relationship of trust recognizing the integrity and independence of the institutions upon which, in large part, the vigor and creativity of the Nation's science depend.

APPROPRIATION REQUEST FOR FISCAL YEAR 1964

At this point, Mr. Chairman, I should like to summarize the significant changes in the proposed budget for fiscal 1964. The total requested appropriation of \$930.5 million for operating programs (excluding construction) represents an increase of approximately 14 percent over the comparable \$817.6 million for 1963. The latter figure requires some explanation. The \$817.6 million is \$63.2 million less than the 1963 appropriation, primarily as a result of two circumstances. One is the showing of comparative transfers in fiscal 1963, amounting to approximately \$38.5 million for activities to be funded next year through appropriations to the environmental and community health programs. The other is the placing of \$25.4 million in unprogramed reserve.

The comparative transfers consist primarily of activities administered by the Bureau of State Services and previously funded from appropriations to the National Institutes of Health. This is in accordance with last year's directive from this committee that these functions be budgeted in the appropriations for the organizational units administering the programs. I should be pleased to submit for the record a brief table which lists these transfers. The unprogramed reserves represent funds which were not specifically programed at the beginning of the fiscal year and consequently were not included in the apportionment allowance. More than 80 percent is in research and training grant funds, and the balance is from direct operations.

I should now like to summarize the major increases in the 1964 appropriation request over the estimated 1963 operating level of \$817.6 million in terms of the functional use of the funds:

Of the total increase of \$112.9 million, \$72.3 million is for research grants. Approximately a third of this increase (35 percent) is for the mental health area and the remainder is for all other Institutes and Divisions. The increase will provide for anticipated additional costs of continuation grants having moral commitments, added requirements for indirect costs (including an allowance for full indirect costs in the latter part of the year), and a small increment for the primate centers. The request would support the same amount of wholly new research projects as did the 1963 budget.

An increase of \$32.2 million for fellowships and training grants will aid in moving toward the training objectives established as a consequence of the report on the Nation's manpower, which I presented last year to this committee. Of the \$32.2-million increase, about 60 percent is in the mental health area and the remainder is for all other Institutes and Divisions.

Collaborative studies in the areas of cancer, mental health, heart diseases, allergy and infectious diseases, and neurological disorders will require an additional \$1.9 million.

An increase of \$1.7 million in funds for review and approval is requested to meet heavier workloads in administering our expanding research and research training grants programs, and to permit further development and strengthening of our management capabilities in connection with these activities.

Finally, a new increase of \$3.1 million has been included for the continued development of direct research activities of the Institutes and for supporting services.

I wish to call your attention especially to the fact that these requested increases include \$9.1 million for support of research and training directed to the problem of mental retardation, following program recommendations of the President's Panel on Mental Retardation, and \$21.5 million for programs to implement recommendations by the Joint Commission on Mental Illness and Mental Health.

Finally, I should like to mention a requested increase of \$840,000 to meet expanding responsibilities of the Division of Biologics Standards. As you will recall, the committee requested in last year's hearings that DBS should receive a separate appropriation. Dr. Roderick Murray, Chief of the Division, will testify for that program.

NIH PROGRAMS IN NATIONAL PERSPECTIVE

Looking toward 1964, Mr. Chairman, I would emphasize that our major efforts will be directed toward these general objectives: (1) Accomplishing the program and administrative adjustments involved in the organizational changes; (2) focusing upon the problems of mental retardation in the broad context of human development, with particular emphasis on prenatal causal factors; (3) expanding substantially our efforts in the field of mental health, notable through grants to support hospital demonstrations and other new studies; (4) further efforts toward the development of scientific manpower and the management of scientific and technical information; and (5) the management and direction of grant programs.

I can say with assurance that the projected operations are organized for greater managerial efficiency, better program balance in grantee institutions, and more thorough exploitation of research opportunities. The three major organizational changes of the past year—creation of two Institutes and a Division for developing our resource programs—express well-considered scientific as well as administrative objectives. One is the consolidation of a broad base of fundamental investigation in medical and health-related sciences to enlarge the reservoir of knowledge from which our categorical operations can draw. Another is the productive stimulus and perspective on human development to be derived from a program in which the entire span of biological and behavioral life can be viewed as a continuum. And the third is the balance and thrust to be gained through a welding of several programs devoted largely to the biomedical needs of the future.

Implicit in all these changes is a concerted effort to emphasize and strengthen stewardship over a dynamic, complex system. This has three aspects: (1) By the very nature of scientific investigation, freedom to pursue ideas and clues into the unknown must be preserved, and the environments conducive to discovery fostered. (2) Emerging concepts and functions demand responsible administrative capability at the periphery, namely in the universities, medical schools, and other research institutions utilizing grant funds. (3) Sound policies must be developed and promulgated, and sound administrative mechanisms instituted by the granting agencies in the interest of effective and prudent use of funds. Our problem, Mr. Chairman, has been to improve administration while preserving the essential conditions of creativity and productivity upon which the conquest of the unknown depends.

Finally, I would say, Mr. Chairman, that we as Federal administrators—as members of legislative bodies as well as health program directors—have come a long way toward recognition of the true requirements for progress in medical

research. It has been clearly demonstrated that the conquest of specific diseases must take place in a context of broad inquiry deliberately acquisitive of any and all knowledge that can be gained of biological and social man. No longer are we narrowly concerned with stamping out an epidemic or even attacking a specific chronic disease. Progress toward the solution of the major health problems of today—problems as complex and long range as cancer, arteriosclerosis, and schizophrenia—demand intensive involvement in ever more fundamental aspects of the life and behavioral processes and full utilization of the great technical advances emerging from the physical, mathematical, and engineering sciences. Of parallel importance has been the recognition that further progress in the life sciences is dependent upon the expansion of the Nation's resources and facilities for this purpose and the strengthening of research and training capabilities of our institutions. Thus, we have come to see our responsibility as that of mobilizing all forces applicable to the task.

The medical schools of this country derive more than half their support from the Federal Government, and the National Institutes of Health is by far the largest contributor. It also supports a major share of the research in schools generally. Although our purpose is medical research and the solution of health problems, we are necessarily concerned with the whole field of science and medicine. This includes such questions as the balance among the sciences, the strength of our educational institutions, and the quality of the Nation's medical care. As Federal administrators we have come to acknowledge these facts. And with this recognition has come a strengthening of interrelationships—Federal-private as well as intergovernmental—through which national scientific policy is made and applied.

A major aspect of our responsibility in this vast system of research support is to foster free inquiry and further the Nation's capability in the life sciences, with a view to continued productivity in the future. Another, no less important responsibility is to pursue these ends with prudent regard for effective and efficient use of the taxpayer's dollar. I am confident, Mr. Chairman, that our plans for 1964 are fully consistent with these goals.

Mr. FOGARTY. Go right ahead.

Dr. SHANNON. Mr. Chairman and members of the committee, it is again my pleasure to appear before this committee in connection with the series of appropriations that finance the program and activities of the National Institutes of Health. In the past, I have always taken advantage of the opportunity presented by my appearance here to report to the committee broadly on the general medical research scene, the events and accomplishments of the past year as well as presenting the general outline of the budget proposals for the forthcoming fiscal year.

I have prepared such a statement for this year's presentation. It is a long statement, but necessarily so in terms of the broad array of activities which comprise the operations of the National Institutes of Health, the many happenings of the past year and the important but diverse aspects of our planned fiscal year 1964 program. However, questions raised by committee members during the Surgeon General's testimony earlier in this series of hearings indicate the need, I believe, to discuss rather thoroughly certain other elements of our programs, their background, and the nature of the research effort in health and medicine.

I should like, therefore, Mr. Chairman, with your permission—which you have already indicated—to present a brief summary of my formal opening remarks with the full statement to be filed for the record. This, I believe, will save the committee's time and provide opportunity for fuller exploration of other considerations relating to our programs.

INCREASES REQUESTED FOR 1964

In the aggregate the fiscal year 1964 appropriation requests for the National Institutes of Health operating programs, now before the committee, total \$930.5 million. This is an increase of \$112.9 million or 14 percent over the comparable 1963 operating level of these programs.

Of this total increase of \$112.9 million, \$72.3 will be utilized for the support of new research proposals through grants as well as to meet the anticipated additional costs of the current program such as increased indirect costs.

Approximately \$32.2 million of the increase will support additional manpower training through fellowships and training grants in line with our objectives of enlarging the national resources of trained manpower in areas relevant to our programs as covered in our report to the committee last year.

Collaborative studies will require an additional \$1.9 million; review and approval activities in connection with the evaluation of grants, \$1.7 million, and the intramural research activities on the Bethesda campus, \$3.1 million. Finally, to meet the expanded responsibilities of the Division of Biologics Standards we are requesting an increase of \$840,000 for that program.

As we discuss the details of this budget in connection with the individual appropriation requests, I believe we can assure you that these proposals constitute a sound plan for further progress in the national effort to understand and control the major diseases and health problems of man.

PERSONNEL AND ORGANIZATIONAL CHANGES

At this point I should like to mention briefly certain personnel and organizational changes which have occurred at NIH during the past year.

May I introduce Dr. Stuart M. Sessoms, to my left, who has succeeded Dr. Price as Deputy Director of NIH. Dr. Sessoms joined the NIH staff in 1953. He served as Assistant Director of the Clinical Center and as Associate Director of the National Cancer Institute, with responsibility for the cancer chemotherapy project. In his new capacity, Dr. Sessoms is giving special attention to the policies and mechanisms of our research support programs in addition to his broad responsibilities as Deputy Director of NIH.

Among the major organizational changes of the past year was the authorization for the establishment of two new institutes, bringing the total number to nine. One of these is the National Institute of Child Health and Human Development; the other is the Institute of General Medical Sciences, formerly a division. The National Institute of Child Health and Human Development will be headed by Dr. Robert A. Aldrich, and the National Institute of General Medical Sciences by Dr. Clinton C. Powell.

One other change that I should like to mention at this point is the creation of the Division of Research Facilities and Resources. Dr. Frederick L. Stone, who has served in key roles in several NIH support programs, is Chief of the new Division.

These new programs will be discussed in full as the committee hears testimony on their proposed budgets.

OVERALL LEVEL OF FEDERAL MEDICAL RESEARCH

I should like now to turn to a series of fundamental considerations relating to the programs of the National Institutes of Health and the Nation's medical research effort in general which I know are of concern to this committee. These matters relate to overall level of Federal funds for this purpose, the productivity of these programs, their rate of growth, the quality of the scientific effort involved and their administration.

Considerable concern has been expressed in many quarters about the magnitude of Federal expenditures for medical research. I think it is always appropriate to challenge the level of Federal activities in any field. In respect to medical research, I think this should be done with the following perspectives clearly in mind:

1. Total Federal expenditures for research and development will reach \$14.9 billion in fiscal year 1964, based on plans in the President's budget.

2. The \$690 million for the support and conduct of medical research encompassed in the 1964 NIH budgets now before this committee constitute less than 5 percent of that \$14.9 billion figure.

3. The great preponderance of the sums for medical research will be expended in obtaining new knowledge for the well-being of man—not the application of known principles in major developmental and hardware efforts.

Relative to productivity, I believe it would be difficult to dispute that over the past 15 years this Nation has brought into being an enormously productive research effort in the medical and health sciences. This development has had a revolutionary influence upon the health sciences, the practice of medicine and indeed the state of the Nation's health. Extension of the survival rates in cancer, open heart surgery, advances in the understanding and control of metabolic disease, reduction in admission rates to mental hospitals, nearly absolute control over many infectious diseases and major extension of knowledge into the basic life processes are significant reflections of this accomplishment. There is promise of even more profound advances in the next decade. Many more specific advances will be brought out in the discussions of the individual programs to follow.

Mr. Chairman, I did not mean to interject any detailed discussion on research accomplishments at this time, but if the committee in reviewing the Institutes' budgets that follow, will turn to pages 9, 10, and 11 of my prepared statement, certain areas of particular importance relative to the advance of science are flagged at that point and you may wish to inquire into them with particular care.

GROWTH OF NIH

Relative to the rate of growth, much has been said about the rapid growth in Federal support of medical research. The general charge is that the increase in funds has been "excessive" and beyond what was required in terms of actual scientific need and opportunity. I do not believe this to be the case. Without question the increases in our programs have been substantial, but this growth has made possible advancing by at least 10 years the state of our scientific knowledge in the biomedical sciences and in our capability to deal with disease and disability. We know and can do now what under the circumstances of growth such as obtained during the early 1950's would not have been available until about 1975. In addition, this growth has made possible a well-balanced program, including broad support for fundamental scientific effort as well as strengthening the research environment and capability of institutions and enlarging the resources in manpower and facilities for the future.

More serious have been the charges of waste and qualitative deterioration in our programs. These allegations, Mr. Chairman, I reject outright. I believe the qualitative character of our programs, the research being conducted under them, and the use of the funds are both reflective of and a measure of the general capability of American biomedical science. It is neither better nor worse than that. The overall character of our scientific activities and the specific projects supported are, by virtue of our non-Federal review and advisory system, the consequence of the best this Nation has to offer in the way of scientific evaluation and advice. I submit that we can do no better. The charges that have been made are general, without any substantive support, and most generally by people who are ill-informed.

ADMINISTRATIVE PROGRESS

I should not like to appear to argue that we are perfect. We are not. We have faced grave and complex problems. We have made mistakes. Being scientists turned administrators, we have perhaps been more concerned and more familiar with the attributes of sound science than efficient administration. I think, however, that we have learned a good deal. In the past 2 years we have made a major effort to adapt and improve our administration practices, our organizational framework, our policies and our procedures to meet the complexity, magnitude and scope of our present program activity. In brief we have undertaken to:

Provide clear guidelines and limits on the use of grant funds for grantee institutions, investigators, and PHS staff;

Establish a formal structure for the development and issuance of grant policy and procedure;

Substantially strengthen internal grants administration;

Develop more highly trained personnel to administer these programs; and

Consult with grantee institutions to assure a full meeting of minds and a clear understanding of the nature of the grant relationship and our respective responsibilities and obligations.

Looking toward 1964, Mr. Chairman, I believe I can say with assurance that our activities are now organized for more thorough exploitation of research opportunities, better program balance and exercise of responsibility by grantee institutions, and for greater administrative effectiveness. I believe it to be clear that further progress in the life sciences depends upon continued support of our ongoing scientific effort, the expansion of the Nation's resources and facilities for this purpose and the strengthening of both the scientific and administrative capabilities of our institutions. Our responsibility is to mobilize all forces applicable to the task. The budget requests now before the committee constitute the measure of needed effort for this purpose in fiscal year 1964.

Mr. Chairman, this completes my summary presentation. I shall be pleased to discuss in detail these and other matters as it pleases the committee.

I might indicate for your information, if you would wish to have it presented, that I have come prepared with some material that might portray graphically the role of our programs, the total scientific scene; the role of Federal versus private contributions; and some of the quantitative aspects of the program that I think may be of interest to the committee.

Mr. FOGARTY. I think that it might be well to go into this rather thoroughly.

Dr. SHANNON. Mr. Fogarty, we have found that charts of this general sort are helpful in explaining some of the details of what obviously is a very complex program, but more particularly in relating our program to other fields of science, and relating the Federal effort to the private effort.

ORGANIZATION

I point out, initially, the organization. The primary thing to be drawn from this first chart is the basic concept of decentralized organization wherein NIH does not play an operational role itself, but operates through a series of constituent institutes.

Mr. FOGARTY. Which one are you looking at now?

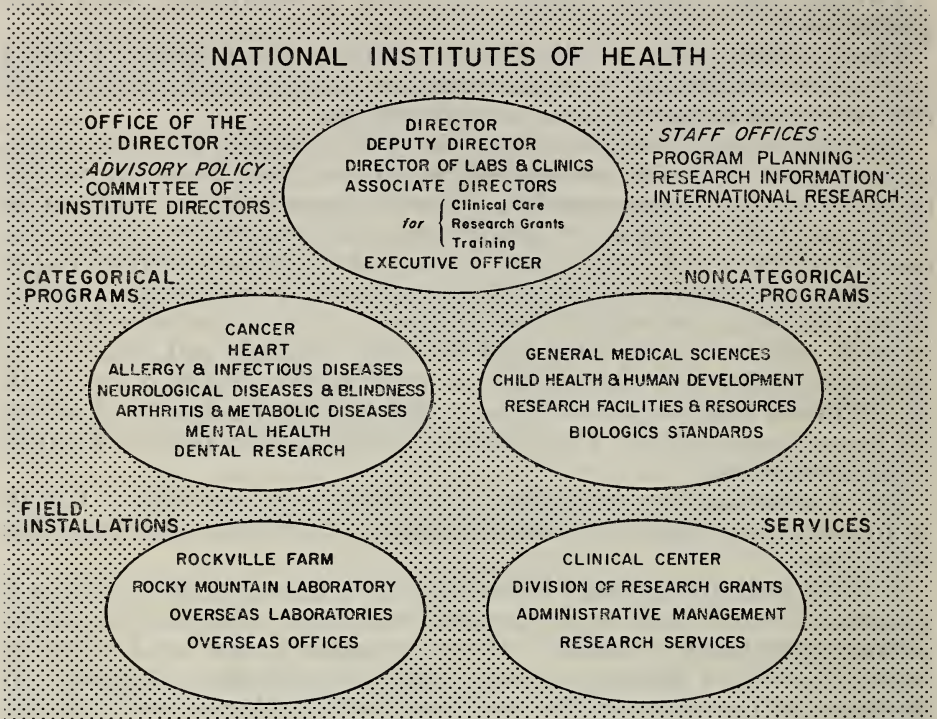
Dr. SHANNON. I will go right down.

Mr. FOGARTY. Oh, the front page?

Dr. SHANNON. On the front page; yes, sir.

I do not think that it would be profitable to discuss organization in great detail. I think most of the committee are well aware of it.

(The chart referred to follows:)

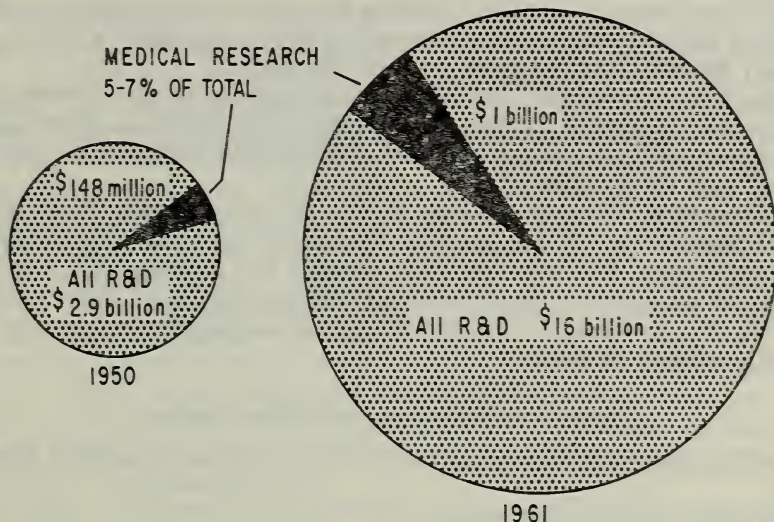


RELATION OF MEDICAL TO TOTAL RESEARCH

Dr. SHANNON. The first chart that I think makes a very important point is chart 2. It is a pie diagram, and illustrates the relationship of medical research as a proportion of all research and development in the United States.

(The chart follows:)

MEDICAL RESEARCH AS A PROPORTION OF ALL RESEARCH AND DEVELOPMENT



Dr. SHANNON. The size of these circles or these pies roughly represent the size of the total research and development in all areas of science and technology in the United States.

The marked increase in size represents an increase from 1950 to 1961 of from \$2.9 to \$16 billion. This is both Federal and non-Federal. This is the totality of research and development in the Nation.

The critical point is that medical research bears a fairly constant relationship to the totality of research in the Nation in this period from 1950 to 1961. Much of the expansion of medical research in this country is in part due to a parallel expansion of physical and engineering research. This reflects the movement into a technical age or new age where science and technology have emerged as one of the more important factors in our national life.

I point out that the United States is not unique in this expansion of technological activities but there is a parallel expansion that has taken place in the northern countries, Norway, United Kingdom, Italy, France, Japan, and so forth.

The order of magnitude in the expansion of all of these countries is pretty much the same.

In some of the countries we have very detailed analyses of both total increase and research development and that which is attributable to the medical sciences. The most recent figures I have seen relate to the United Kingdom where the percentage of the gross product

that goes into research and development and the proportion of research and development that is attributable to medical research is almost identical or the same order of magnitude, put it that way, as in the United States.

We do not have as detailed figures for some of the other advanced countries, but these are in the process. In the aggregate, though, they probably would turn out pretty much the same.

So we can see that the United States is sharing in the development, the rapid development of this technological age which is international in character and must be considered as one of the important factors in national and international life.

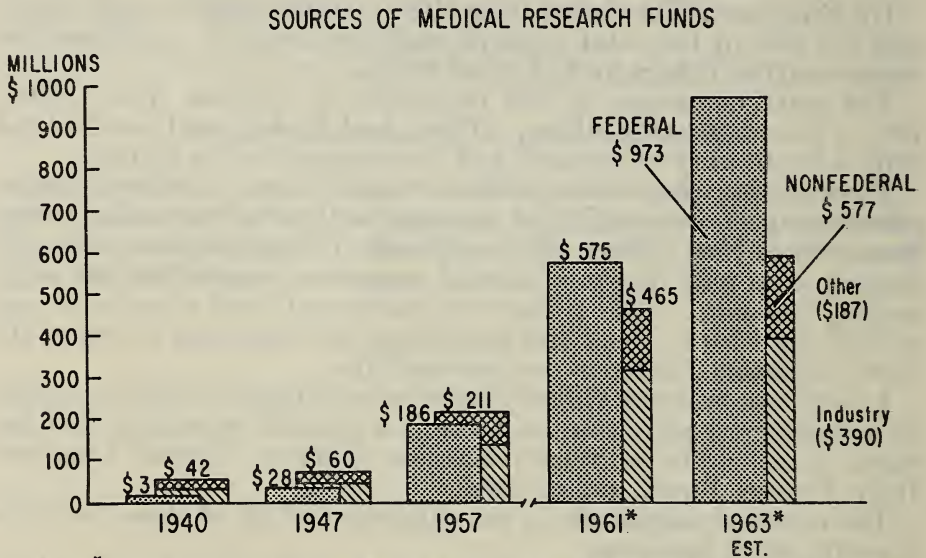
Mr. FOGARTY. The second one shows the percentage of dollars in medical research in 1950 is just about the same as 1961, is that right?

Dr. SHANNON. Yes, sir. Rather than it having been an explosion in medical sciences as such, medical science has kept pace with the very rapid acceleration of technological advances in science that generally affects all fields.

SOURCES OF MEDICAL RESEARCH FUNDS

The third chart shows an analysis of the sources of medical research funds.

(The chart referred to follows:)



Dr. SHANNON. There are a series of pertinent lessons to be drawn from this chart. In the first place there is a pronounced expansion of medical research, of which you are aware, in the chart analyzed here.

The pertinent factor, however, is in contrast to all other areas of research and development in the medical sciences increases in support from private sources parallel increases in support from Federal sources. In point of fact contrary to 1947, there was basically no Federal support of science in biology and medicine save that which was done in Federal laboratories. This marked the real beginning of the grant program. But in the past decade or so, the order of magnitude of the increase of support of the medical sciences from non-Federal sources has not been unlike the Federal. In other words, both have increased very substantially. This is not to say that there has been no change in their relative position. Federal support is now the dominant factor.

Now, the lesson to be drawn from this is that the establishment of a broad centralized operation for the support of medical science in this country as the result of the expenditure of the Federal dollar has in no sense dried up support of medical science from other sources. If anything it has stimulated it.

Secondly, contrary to the other sciences where there has been a withdrawal of private funds in support of science, the very nature of the private contributions to medical research, both industrial and personal, indicated the determination on the part of the American people through research to find better health.

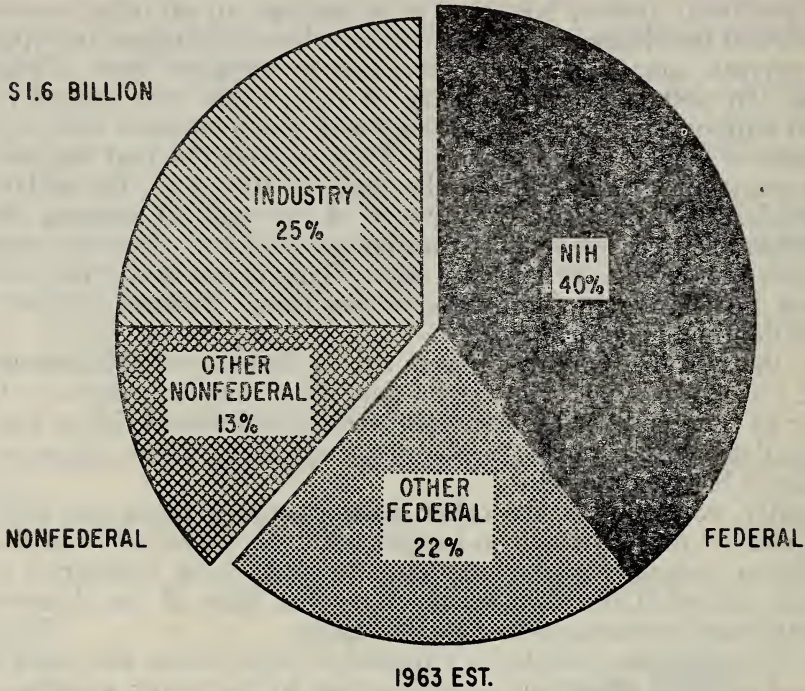
Now here we have people in a period of time where tax costs are high and yet year after year contributions to voluntary agencies increase. I see no indication that there has been any lessening in the thirst of the American people for better health through research. This places a very great responsibility on those expending research dollars.

NIH PORTION OF MEDICAL RESEARCH SUPPORT

Dr. SHANNON. Now, the next chart has a very special amount of significance to the programs of the National Institutes of Health.

(The chart follows:)

NIH FUNDS AS A PROPORTION OF NATION'S MEDICAL RESEARCH SUPPORT



Dr. SHANNON. This shows a pie diagram broken up into four segments which relates to the source of funds for medical research. And you notice these actually are 1963 current figures. NIH supports 40 percent of all medical science in this country; other Federal agencies, 22 percent; industry, 25 percent; and other non-Federal agencies, 13 percent.

Now, when you realize that the industrial enterprise is limited to the pharmaceutical industry which in general, focuses its research activity upon its manufacturing objectives, then the contribution of NIH for support of all medical research in this country becomes increasingly important.

It then becomes by and far the dominant influence in the support of the biomedical sciences across the Nation in these fields.

A lesson to be drawn from this fact is that it is within our capabilities to influence the biomedical sciences for the better or for the worse, depending upon our wisdom in program development, and depending upon the terms and conditions which relate our activities to the centers of higher education across the Nation.

Dollarwise, we are in a position, providing mechanisms are unsuitable, to adversely dominate this area of science. I would hope we are never placed in a position through restrictive legislation or otherwise where strictly bureaucratic consideration becomes the determining factor of how this large sum of money shall be spent.

I think we have a broad responsibility to indicate target areas, to indicate or to be certain that there is a reasonable distribution across important fields.

I think we have the responsibility to be certain that the Federal dollar is expended for the purposes for which it was appropriated.

I would hope we are never in a position where our control mechanism so invaded the sanctity of our institutions we support that we are disruptive of the practices and well-being of these university worlds upon which in the long run our Nation must depend.

So to summarize then, this chart emphasizes the obligation of the NIH to exercise mature thought, sound administrative procedures, but also sound administrative restraints in exercising such broad potential control over such a large segment of science.

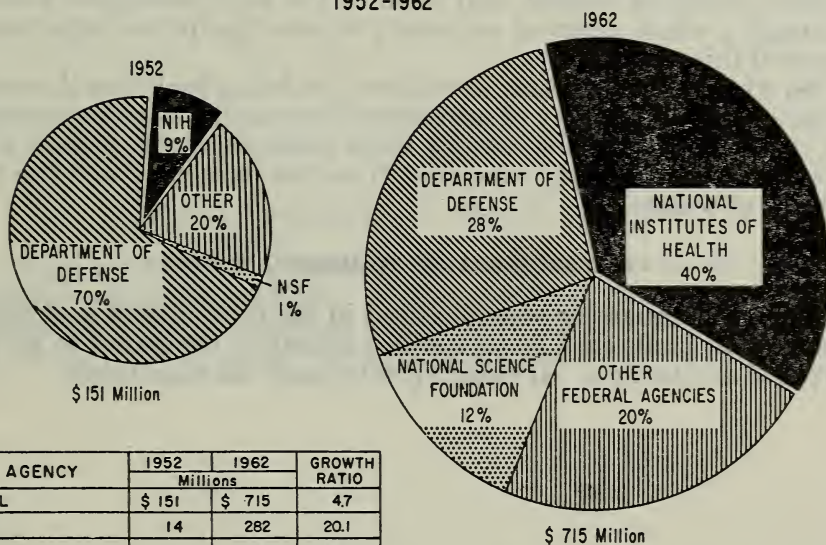
FEDERAL SUPPORT AT UNIVERSITIES

Dr. SHANNON. Now, this gives another breakdown that may surprise the committee.

This shows trends in Federal support of research at colleges and universities.

(The chart follows:)

TRENDS IN FEDERAL SUPPORT OF RESEARCH AT COLLEGES AND UNIVERSITIES
1952-1962



AGENCY	1952	1962	GROWTH RATIO
	Millions		
TOTAL	\$ 151	\$ 715	4.7
NIH	14	282	20.1
NSF	1	86	86.0
Defense	106	201	1.9
Other Federal	30	146	4.9

Note: Excludes university-managed Federal contract research centers, such as Los Alamos, Argonne, and Jet-Propulsion Laboratory.

Sources: National Science Foundation and NIH

Dr. SHANNON. Now, this is all research, physical as well as biological and medical.

In 1952 you will see that research expenditures within our institutions of higher learning were primarily dominated by the defense dollar at which point in time roughly 70 percent of all federally supported science in our schools and universities was contained within the appropriation of the Department of Defense.

Now, as these programs have grown, the actual dollar value of the defense support has increased; but it has lost its dominant position and at the present time the two dominant agencies are the National Science Foundation, the National Institutes of Health, and within a year or two we will be joined by a third agency which will be the Space Agency.

The programs of these agencies are all essentially civilian, civilian motivated, nondefense type activities.

Now, this, in addition, shows another factor that is not commonly appreciated.

When we think of medical research, we too frequently think of research in the medical schools and equate the two together, or research in the hospital and equate this with medical research.

But with the progressive development of new instrumentation and a more penetrating view of the underlying fundamentals of biology and their relevance to health and disease, it now becomes possible to obtain searching insight into some of the basic biological processes, through a whole array of university science disciplines, significant to areas of this sort.

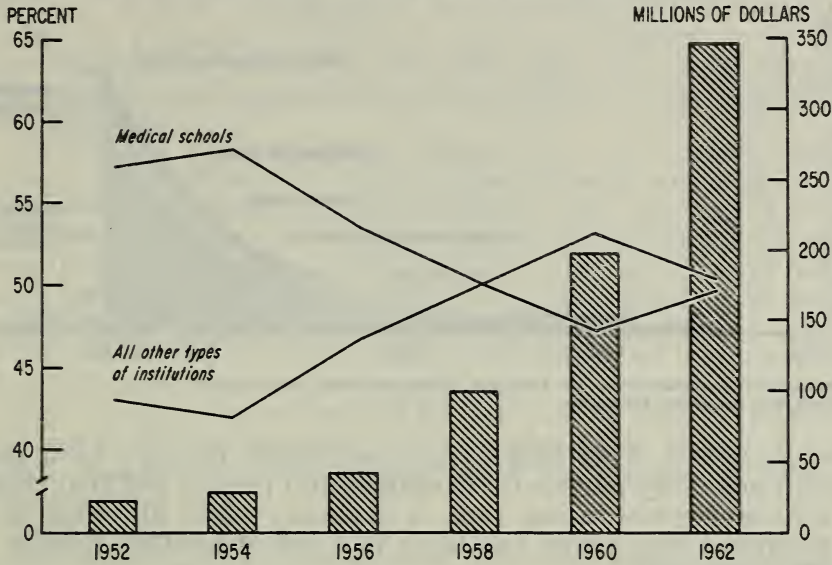
So what these programs have done is to bring back into the medical sciences the whole array of university sciences that were lost contact of in the early part of the century when medical schools became highly specialized and largely separated from the university and the mainstream of science.

RESEARCH GRANTS TO MEDICAL SCHOOLS

Now, this generally is emphasized in the next chart where the percentage of funds that go to medical schools is compared to all other types of institutions. It reflects pretty much the same thing.

(The chart follows:)

HALF OF NIH RESEARCH GRANT FUNDS GO TO MEDICAL SCHOOLS, HALF TO OTHER INSTITUTIONS

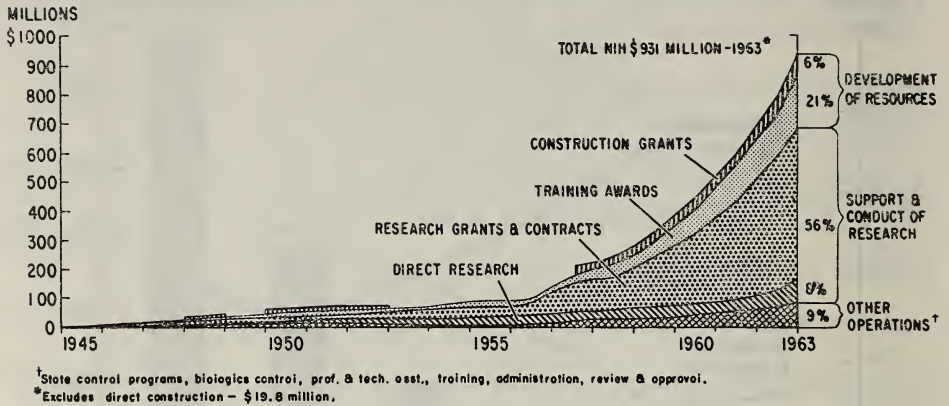


NATIONAL INSTITUTES OF HEALTH GROWTH

Dr. SHANNON. In the aggregate, the next chart shows the growth in relation to functions of NIH. This is about a 20-year period, where our programs went from a point on this chart that it is difficult to read quantitatively to the top of the scale, which approximates \$1 billion.

(The chart follows:)

NIH-GROWTH AND FUNCTIONS



Dr. SHANNON. This broken up would show that we have gone through some very purposeful developmental periods and that this is not a heterogeneous scatter type of explosion where all elements of our programs have grown like topsy in a sort of headless fashion, as has often been said.

I point out the striking changes in the program. Very important is the leveling off in and around 1955, where, after an initial growth, the program beginning after the postwar period there was for a period of 2 or 3 years a fairly constant program.

This, I might indicate, was in part a consequence of the Korean war and part a consequence of a wide variety of other problems related to the Federal budget.

But in 1957 with a new Secretary of Health, Education, and Welfare, Dr. Folsom—you have talked long with him on many occasions, Mr. Chairman—we spent the better part of the summer of 1956 in a very careful analysis of the program of the National Institutes of Health.

As a result he reached the judgment that the funds expended for medical research at that time were grossly inadequate both in terms of the opportunity and in terms of the breadth and importance of the problem, and he recommended an unprecedented increase of our budget; he stated at that time he thought the limitation on the rate of growth in medical sciences should be the rate of development of scientific personnel and resources, not the availability of the absolute number of dollars.

This budget was taken by the House and by the Senate, the principles roundly endorsed, and we came out with substantially more than even Dr. Folsom had recommended. This was fiscal year 1957.

This basically was the turning point in the programs of the National Institutes of Health and since that time, the attempt has been made on the part of the Congress, as we interpreted it, to have the medical sciences supported to the point where the limitation on growth is the availability of scientists, the availability of resources, rather than be determined by dollar expenditures.

Now, as the program beyond the summer of 1956 developed, you will see in the new segments which develop on the chart.

Mr. FOGARTY. You are talking about the summer of 1956; that would be fiscal 1957.

Dr. SHANNON. Fiscal 1957.

The next year for the first time, the stable program for research facilities construction was started.

You see an abrupt widening of the bar diagram here—whatever you call this type of diagram—that relates to the event, as well as the substantial increase in funds for the conduct and support of research.

So this leads us to a program now where support and conduct of research amounts to 64 percent of the total program, where 27 percent is devoted to the development of resources, and where all other operations in our budgets are 9 percent.

When I say "all other operations," I have in mind State control programs, biologics control, professional and technical assistance, training, administration, review and approval and the like.

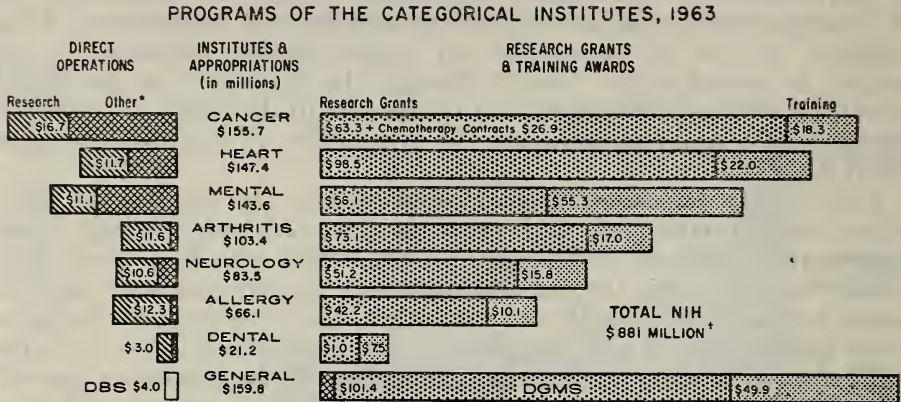
It is not commonly appreciated that roughly, if I can use growth figures to make the point; for \$2 spent in support of current research, approximately \$1 is spent on resources for the future; precise figures 64 and 27 percent.

I think on this when there is talk about the rapid growth of our program. One must realize that this relationship between very heavy investment in the future while at the same time there is broad support of current research is what has permitted the programs to grow without sacrifice of quality.

CATEGORICAL INSTITUTE PROGRAMS

If one turns then to the programs of the categorical institutes, this gives the categorical breakdown as the appropriations are spread in 1963; it shows the relative sums.

(The chart follows:)



* Professional & technical assistance, state control programs, review & approval, training, administration.

† Does not include \$50 million for construction grants or \$19.8 million for direct construction.

Dr. SHANNON. In the heavy lines, looking to the right, the heavy dots are support of research; the lighter dots support of training by appropriation.

I would point out again in consequence of decisions reached in 1957, summer of 1956, it was decided to take out of the categorical institutes many functions that might better be done on a non-categorical basis.

This resulted in a planned development of the Division of General Medical Sciences, not as a service organization of the other categorical institutes, but as a centralized point for support of both research and training in those science areas which were not truly categorical in nature but which had relevance to all categorical areas. Thus, this growth which now brings this division in 1963 to the point of being our largest activity, again is the consequence of the careful plan that took place in the summer of 1956.

Again I would emphasize the evidence of planned development as opposed to frequent references to our growth being like "Topsy."

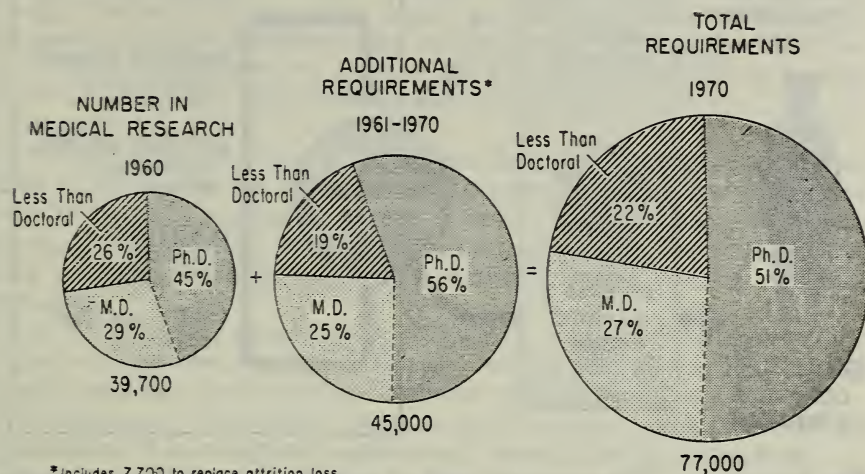
MEDICAL RESEARCH MANPOWER

As we look into the future we feel that the medical sciences will continue to prosper largely depending upon the extent to which we can satisfy our needs for superior type of manpower.

These needs are quantitative. The quantitative figures are reflected in these pie diagrams. We need M.D.'s, we need Ph. D.'s, and we need many people who are nondoctoral.

(The chart follows:)

MANPOWER FOR NATION'S MEDICAL AND HEALTH-RELATED RESEARCH BY DEGREE 1961-1970



Dr. SHANNON. Our ability to get these people in no small measure will be determined by the attitude of the Federal Government toward development of people in these general categories.

For example, we will not make up our requirement for M.D.'s in 1970 short of expansion of our present plant for the development of physicians.

At the present time we are taking into research and academic medicine about 8 percent of all graduating physicians.

Were we to roughly double the take at present levels of the production of physicians we would probably be impairing the availability of physicians to the people.

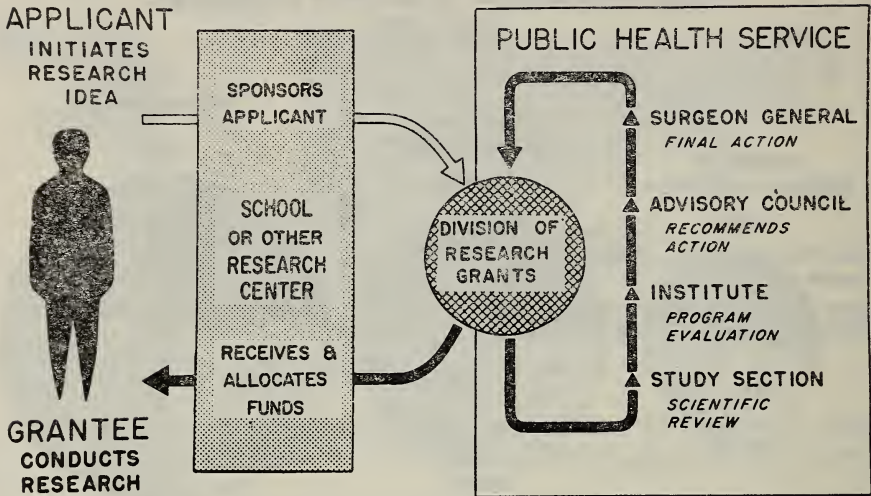
In the Ph. D. category, as we pointed out in our manpower document last year, it becomes quite apparent we are beyond the point where our personnel needs can be satisfied with simple diversion to medical research of wholly trained people, we must directly participate in the basic training of these scientists.

RESEARCH GRANT PROCEDURE

Now, I have sketched here—and, Mr. Lesinski, this is particularly what you asked for—how a research grant is made—if I can take a typical research grant as an example of how general judgments relative to grants are made:

(The chart follows:)

HOW A RESEARCH GRANT IS MADE



Dr. SHANNON. The same process or a somewhat analogous process would obtain for our fellowship program, for our training grant program, and the like, each somewhat different because they are for a different purpose, but in terms of the principles involved, they would have the same procedure.

There are several important points that I would like to emphasize here. I would like for you to bear in mind that our grant programs in general depend upon the basic concept that worthwhile scientific activities to be undertaken arise not in the mind of the Administrator in Bethesda, but rather in the scientist's mind and environment in which he works.

Assuming that a scientist has a stable scientific environment, that he has adequate training, that he has adequate resources, and his institution will sponsor his application, he has the ability to apply to us for support to do things he feels are scientifically important as far as he is concerned.

Whether the work be relevant to heart, cancer, or the like, he is not concerned about that point.

This application comes to our Division of Research Grants.

On arrival, an appraisal is made whether the piece of work proposed in the application is in fact more relevant to heart, more relevant to cancer, or more relevant to, say, mental health. Based on this judgment an assignment is made to the institute that has appropriated funds to support the work proposed.

But at this time the grant is not submitted to that institute for action; it is retained within the Division of Research Grants, a copy is sent for informational purposes to the institute concerned.

The next step in the grant process is that the application goes to a study section for scientific review.

Now, all grants do not go to a regularly established study section, although the bulk of them do. Many grants are sufficiently complex as to require the establishment of special study groups for their review. Such special review groups have been formed for a limited number of programs and actually for individual projects if they are large enough.

But in all cases the Division of Research Grants accepts the responsibility of giving advice to the council concerned of a purely technical nature as to the competence of the scientist, the adequacy of his resources, the conciseness with which he can visualize his problem, the merits of his proposal, and the reasonableness of his research approach.

Thus, in reaching conclusions, there is a combined judgment that includes also an evaluation of the net worth of the scientist on the one hand and net worth of the scientific environment on the other.

One judgment is that the work is good science, and it should be supported, or it is not good science and should not be supported.

The second judgment, assuming the work is considered supportable, involves ranking the application in respect to its relative merit in comparison with other applications that are before the review group at that time. This is what we call the priority system.

Each member of the study section assigns by individual vote a rating. The final priority rating of the application is a simple average of the individual ratings. The highest rating in such priority that one can get is 100; the lowest is 500, but even an application receiving a rating of 500 has had a preliminary recommendation by this group that the work should be supported.

Now, this priority rating is useful to the Council. They do not necessarily follow them blindly. But, as is usually the case in appropriations where funds are not available to pay all research grants, the priority gives a relative ranking as best one can do of relative merit.

The research grant application then goes to the Institute for program evaluation, together with the study section recommendation for approval or disapproval—and the priority.

Institute staffs undertake program evaluation of the application so that in discussing this particular project with their council, they can point out where this proposed activity fits in the overall scale of things as far as the institute is concerned.

Now, I do not want to overdraw this, because the council does not look at every individual application in this degree of detail; but this analysis by staff of the relative role of such proposals in the overall program of the Institute, particularly in respect to new grants, permits the council to determine where relative emphasis is going, assuming certain actions are taken.

In the light of these considerations, the Advisory Council then recommends to the Surgeon General whether to approve or disapprove the grant application.

The Surgeon General cannot make a grant for a project unless the council recommends such action.

If the council recommends it, the Surgeon General does not have to make it. So he can take a negative action, but he cannot take a positive action without council recommendation.

Always, when a grant is made, the general order of magnitude of the dollar commitment is indicated and even more now than previously, this is subject to further negotiation with the actual grantee in order to determine the specific dollar amount. Commitments of support for subsequent years are frequently made in connection with the award of grants which, with all other things being equal and annual appropriations being available as they have been in the past, constitutes moral commitment against next year's appropriation for continued support.

Through this process, investigations are not turned on and off on an annual basis.

We do not support anything less than 2 years. If we cannot support it that long, we feel that probably he should go elsewhere for support for a shorter period of time.

We try to provide a time period of support that will bring the individual to an adequate point where he can make a substantial scientific contribution which in turn can be assessed as a basis of determining further support action.

The individual reports to us on an annual basis. I would emphasize the annual reports are not in great detail because in most of these research programs, the grantee tends to overdraw his conclusions.

On the other hand, if the grant comes up for renewal, then the progress report is in great detail and the investigator's future needs are determined at that time.

So I think in general we have a system that, as far as humanly possible—scientists, after all, are human—assures the maintenance of a sound program.

These commitments of large sums over several years are a result of the expenditure of a series of smaller sums reviewed by us with a high degree of seriousness.

I think the impression conveyed by these data tends to confuse the committee. We live with these figures today, day in and day out. I was thinking when you were commenting on the size of the cancer program the other day and I said maybe 2,000 grants would seem like a very large number of people, I thought it might be worthwhile if I would take somewhat smaller size figures and attempt to explore them with the committee—particularly with you, Mr. Chairman, and with you, Mr. Lesinski—I might say if you want to return to that earlier conversation, we would be glad to spend the time.

NIH GRANTS WITHIN SELECTED STATES

The national figures are very large, and I think unless you live with them on a day-to-day basis, these figures are less meaningful to the committee than they are to us. But I think when you go from a national picture to a State, within a State, and begin to recognize institutions and scientists, you begin to understand the role they play in the community life. They are the source of a good deal of our

professional people; we know the shortages. We know particularly the States where they have universities.

So I asked our analytical group to prepare for me the information for the States for each of the members of the committee, a total analysis of our operations in each of the States concerned. I will not go into great length, but I thought the committee would be interested. Our ability to do this, sir, is because we do use electronic data processing equipment and one can pull out this type of analysis.

For the State of Michigan, for example—this is the compilation of the research grants from NIH to the State of Michigan—it seems like an awful lot, but these range from a small college that has one grant, which is a place called Alma College, to one of the older scientific institutions in the Nation; namely, the University of Michigan.

Mr. LESINSKI. At that point, Mr. Chairman—may I say if you think you will scare me by these figures, you do not.

Mr. FOGARTY. No. The point Dr. Shannon is trying to make is that the overall figures are hard to comprehend.

Dr. SHANNON. That's it, sir, hard to comprehend.

Mr. FOGARTY. And Members have a special interest in their own State.

Mr. LESINSKI. What is the sum total of Michigan?

Dr. SHANNON. I do not have the figures broken out that way, sir, but I can get it for you.

I have the total by Institute. For example, the National Institute of Allergy and Infectious Diseases has 20 grants in the aggregate of \$224,000; the National Institute of Arthritis and Metabolic Diseases has 55 grants in the aggregate of \$952,000; the National Cancer Institute has 29 grants in the aggregate of \$554,000; the National Institute of Dental Research has 11 grants in the aggregate of \$214,000; the Division of General Medical Sciences has 32 grants in the aggregate of \$185,000; the Division of National Heart Institute has 22 grants, \$944,000; the Mental Health, 33 grants, \$1,200,000; for the Neurological Disease and Blindness, 34 grants, \$642,000.

Now, I do have a figure I did not realize; I have the University of Michigan receiving from NIH 239 grants in the aggregate of \$7,167,000.

Mr. LAIRD. You may not have scared Congressman Lesinski, but you sure impressed me.

Dr. SHANNON. I have a comparable analysis for Wisconsin.

Now, the designations in the last column are the departments within which this work is done.

What is to be drawn from this is that at the present time, in the medical sciences, medical research is largely made up of the individual efforts of individual scientists. Unfortunately, it is only in those areas where the target can be easily visualized that the engineering type of research is being done. To supplement this presentation I have asked Dr. Endicott, and he will be an early witness, to take the totality of his cancer program and divide it up into grants for research, training, fellowships, and the like; to take the grants for research and show that which is self-generated, a research grant such as this, that which is organized, highly organized, that which is done under contract, and break it down by field of activity.

When you go through one of those analyses, I think you only have to do it with one Institute, then I think you will begin to get a feel for the fabric of science.

Mr. DENTON. Do you have this for everybody?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. Dr. Shannon, in regard to these charts, I have just one or two questions.

Dr. SHANNON. Yes, sir.

RESEARCH SUPPORTED BY DEPARTMENT OF DEFENSE

Mr. LAIRD. This chart is not numbered but it is the chart with two pies on it. For 1962, you show that the Department of Defense accounts for 28 percent of the Federal support of research at colleges and universities. You have a footnote regarding certain exclusions.

I can't believe that chart is right because as I have studied the Defense budget, I have gained the impression that the Department of Defense probably contributes even more than you do.

Dr. SHANNON. Well, let me explain what the exclusions are. The exclusions are for wholly run contract research institutes.

MIT has a laboratory which is not part of the educational process, Cal Tech has a jet propulsion laboratory which is not a part of the educational process—these are really university-managed research centers.

Mr. LAIRD. What about the Army research centers? These are located on university campuses. There are big expenditures in this area.

Dr. SHANNON. There are large expenditures but they are not part of the educational process, whereas the Defense grants contained in chart No. 5 are part and parcel of the university department structure.

Mr. LAIRD. You have just grants in here?

Dr. SHANNON. No; grants and contracts; but grants and contracts exclusive of federally run or specially contracted research institutes.

Now, we have that analysis too, we will give you that analysis in parallel.

These are sufficiently small in number, although very large in dollar size, they are very easy to keep track of.

BREAKDOWN OF TOTAL EXPENDITURES FOR MEDICAL RESEARCH

Mr. LAIRD. Perhaps this would be a good place to put in the record a breakdown of the total funds being spent this year and each of the last 2 years, broken down between private and Government spending and showing a breakdown of the Federal part by agency. Could that be done?

Dr. SHANNON. Certainly. We will supply that.

(The requested information follows:)

Federal expenditures for performance of medical and health-related research, fiscal years 1961, 1962, 1963¹

[In thousands of dollars]

Agency	1961 actual			1962 actual			1963 estimate		
	Total	Budgeted	Directly related	Total	Budgeted	Directly related	Total	Budgeted	Directly related
Total	\$574,860	\$464,277	\$110,583	\$774,294	\$631,996	\$142,298	\$872,742	\$785,288	\$187,454
Atomic Energy Commission	55,664	6,919	48,745	64,706	6,930	57,776	75,556	7,722	67,834
Federal Aviation Agency	1,726	1,726		1,785	1,785		2,801	2,801	
National Aeronautics and Space Administration	4,850		4,850	12,988		12,988	38,150		38,150
National Science Foundation	11,775		11,775	15,300		15,300	17,300		17,300
Office of Emergency Planning	471	471							
Tennessee Valley Authority	na	na	na	214		214	267		267
Veterans' Administration	18,447	18,447		26,834	26,834		29,441	29,441	
Department of Agriculture	17,842		17,842	22,268		22,268	22,500		22,500
Department of Commerce	na	na	na	335	31	304	363	32	321
Department of Defense	48,026	21,540	26,486	64,209	31,064	32,545	81,323	41,534	39,789
Department of Health, Education, and Welfare	414,392	414,392		563,752	563,752		702,618	702,618	
National Institutes of Health	(375,421)	(375,421)		(495,391)	(495,391)		(624,464)	(624,464)	
Department of Interior	885		885	903		903	1,203		1,203
Department of State	782	782		1,000	1,000		1,140	1,140	

NOTE ON COVERAGE AND SOURCES.—The statistics shown above—actual obligations for fiscal years 1961 and 1962 and estimates for 1963—were reported by Federal agencies to NTH following a review by each agency of its research activities to show explicitly obligations for all medical and health-related research in all fields of science (biological, medical, agricultural, psychological, physical, mathematical, engineering, social) distinguishing between (1) funds separately budgeted for medical and health-related research, specifically identified, programmed and justified as such, and supported for the purpose of improving human health (all the research activities of agencies or subagencies whose sole mission is advancement of human health through research may thus be included); and (2) funds for research directly related to health in terms of substance or probable application, but which derive from funds budgeted, justified or supported for purposes other than medical or health objectives (for example, the general support of science, the promotion of agriculture, the achievement of the Nation's strategic objectives in outer space). As the table shows, almost 20 percent of the total represents this latter category of research

directly related to health but supported for other purposes. An analysis of the data collected in a similar survey conducted last year is presented, in "Federal Expenditures for Medical and Health-Related Research, 1960-63," Resources for Medical Research, Report No. 1, August 1962, PHS Publication No. 969.

Federal agencies have been requested to provide NTH with data consistent in scope and coverage with the statistics shown above, for the 1947-60 period. An analysis and review of these data will be published in the spring of 1963, providing a comparable time series for the 1947-63 period.

¹ Coverage is limited to conduct and support of medical and health-related research. Support of other activities such as training or capital outlays for research facilities is not included in this series.

Source: Resources Analysis Branch, Office of Program Planning, NTH, December 1962.

*National expenditures for performance of medical and health-related research by
source of funds, fiscal years 1960-63¹*

[In millions of dollars]

Source of funds	1960 actual	1961 actual	1962 estimate ²	1963 estimate ²
Total	\$830	\$1,040	\$1,290	\$1,550
Government	467	605	811	1,018
Federal	444	575	774	973
State and local	23	30	37	45
Industry	250	311	345	390
Private support	113	124	134	142
Foundations and health agencies	68	72	77	80
Other private contributions	12	15	18	21
Endowment	19	19	19	19
Institutions' own funds	14	18	20	22

¹ Coverage is limited to conduct and support of medical and health-related research. Support of other activities such as research training or capital outlays for research facilities is not included in this series.

² Data on Federal obligations are available at the beginning of the fiscal year. Firm data on non-Federal expenditures cannot be obtained until after the end of the fiscal year. Therefore, the estimates for 1962 and 1963 may overstate the Federal share. These data are subject to revision pending analysis of 1962 and 1963 research expenditures by hospitals, State Governments, medical schools, universities, and research institutes.

NOTE.—The estimates shown above reflect significant improvements in the scope and coverage of national expenditures for medical and health-related research. Statistics for years prior to 1960 are, therefore, not directly comparable; the time series for the back years will be revised as soon as possible.

The significant revisions are as follows: In the government sector, both the coverage and method of measuring Federal agency obligations for medical and health-related research have been improved to reflect research, in all fields of science, that is medically related, distinguishing between research obligations budgeted and justified for health purposes, from obligations for research directly related to human health but supported for other purposes; the data for Federal agencies were obtained by the National Institutes of Health through a survey conducted by that agency at the request of the Bureau of the Budget. (An analysis of the data collected in a similar survey conducted last year is presented in "Federal Expenditures for Medical and Health-Related Research, 1960-63," Resources for Medical Research, Report No. 1, August 1962, PHS Publication No. 969.) Support for medical research provided by State and local governments now includes appropriations made directly to education institutions and hospitals for the performance of medical and health-related research. In the industry sector, coverage has been expanded to include, in addition to the research expenditures of the pharmaceutical industry, comparable data for the medical supply industry provided by the Bureau of the Census and the National Science Foundation, and data for the medical electronics industry obtained by NIH. In the nonindustrial private sector, a comprehensive survey was conducted, through the cooperation of the National Science Foundation, to obtain benchmark data on the support of private foundations for medical and health-related research for 1960. (See "Foundation Expenditures for Medical and Health-Related Research and Education, 1960," Resources for Medical Research, Report No. 2, November 1962, PHS Publication No. 983). The estimates for the 1961-63 period for this sector are derived from a system of continuing and more complete reporting both from the source of funds, and from the performer.

Source: Resources Analysis Branch, Office of Program Planning, NIH, December 1962.

NOTIFICATION OF MEMBERS CONCERNING GRANTS

Mr. LAIRD. In your last chart, Dr. Shannon, I notice that you have eliminated one step in this graphic display of what happens to a research grant.

Dr. SHANNON. What was that, sir? What step?

Mr. LAIRD. I discussed it with you last year on page 184 of our hearings; that is, the notification of a Member of Congress from the particular district in which the grantee is located. I commend you for eliminating this step.

Dr. SHANNON. Fortunately it was possible to eliminate this in no small measure because of the discussions in last year's hearings.

Mr. LAIRD. Very good.

Mr. FOGARTY. Are there any other questions?

Mr. LAIRD. Not on these charts.

Mr. FOGARTY. Mr. Denton, do you have questions concerning these charts?

SOURCES OF MEDICAL RESEARCH FUNDS

Mr. DENTON. I just want to ask, in connection with the third chart, what other Federal agencies are investigating health?

Dr. SHANNON. Atomic Energy, State agency, Department of Defense, Agriculture, Veterans' Administration, these would be the major ones; National Science Foundation.

Mr. DENTON. Now, you have "others." Does that "others" embrace private charities?

Dr. SHANNON. Yes, hospital endowments, university endowments, State contributions and the like.

Now, Mr. Denton, if you would pause there for a moment, I would like to make a point; if you would take that last bar (chart No. 3), it again emphasizes the importance of very carefully perceived grant procedures, because, as far as the university groups are concerned upon which we depend for the development of our scientists and our physicians and the like, the main interplay is between this bar of non-Federal expenditures and this bar which is Federal expenditures. So that in the university environment, we support much more than 40 percent of medical sciences.

Mr. DENTON. What percentage of "others" would you say private charity embraces?

Dr. SHANNON. I would say probably the majority of it, because endowment in this contribution research is very small now.

Mr. DENTON. What do you mean by "endowment," Rockefeller Foundation?

Dr. SHANNON. No, sir. University endowment—let me put it this way:

Those funds that come from interest-bearing notes or securities or investments that are made from capital made available to a school or university.

Now, I would draw this contrast. In the twenties, the bulk of all research was from such endowment funds; but now with the lesser return on endowment, with our income tax system, involved as it is, the ability for individuals to retain moneys for purposes of setting up these large endowments is essentially nil and—without quarreling with the wisdom of our tax system—this forces new programs to look to the Federal Government rather than to the private dollar.

Mr. DENTON. Somebody gives a certain sum of money for endowment to some university for them to carry on a certain type of research?

Dr. SHANNON. Yes, sir. That would be non-Federal.

EARLY MEDICAL RESEARCH PROGRESS

Mr. DENTON. Here is a question I am asked a great many times:

Looking at that chart, take the year 1940, very little was spent for research.

Dr. SHANNON. Yes, sir.

Mr. DENTON. And compare that with 1961 and 1963; see how much is spent now?

Dr. SHANNON. Yes, sir.

Mr. DENTON. Now, medical science did make a great deal of progress up until 1940. How did they do that without research funds such as we have now?

Dr. SHANNON. Well, in the first place, progress was very slow because you are talking now about a period of time when I was working as a scientist, not an administrator, so I can speak very freely.

The pace of science, pace of scientific development was very slow.

Mr. DENTON. It what?

Dr. SHANNON. The pace of scientific development was very slow. The number of scientists that worked were very small.

The rate of development today is of a completely different order of magnitude.

And I think that I could answer your question in part by saying you can look back to the year 1900 and in the period from 1875 to 1900, there were broad advances in science, there was the recognition of infectious diseases, there was a beginning of public health methods;

but at that time, there were scarcely any research institutes in this Nation.

There was Hopkins, Rockefeller Foundation, Carnegie Corp., the University of Michigan, the University of Pennsylvania, and Harvard. These were the only medical environments; yet progress was made.

So I do not think you can just look at the size and say, well, progress was being made there. How does that compare with progress being made now?

The pace in 1940 was a different order of magnitude than the pace in 1900, the pace in 1963 is of a different order of magnitude than the pace in 1940, and it, roughly, I think, reflects the dollars being spent.

RESULTS OF MENTAL HEALTH RESEARCH

Mr. DENTON. Having been on this committee, I have noticed a great deal of progress has been made in the last 10 years.

Dr. SHANNON. Yes, sir.

Mr. DENTON. Especially in mental health. I don't want to get into details at this point but would you give a few overall remarks?

Dr. SHANNON. I think the most striking thing—I know when Dr. Felix is here, he can talk about progress in terms of progressive decrease. The census of medical hospitals was supposed to have projected an increase. I think this is important. But I think in part this reflects not only new tools but an enlightened attitude.

I would rather take another area that has been studied extensively, quite well understood in the 1920's, 1930's, and certainly the early 1940's. I have in mind the cardiovascular disease, strokes, cardiac failure, coronary artery disease, thrombosis, and the like.

Well, despite the fact that heart disease will always have an extraordinarily high mortality rate, because, basically, this is too frequently a terminal event, nonetheless the American Heart Association has been able to show in their analysis a continued progressive reduction in case fatalities due to the important disease of hypertension, arteriosclerosis.

This is in an area where neglect is not characteristic, where systematic studies have been going on. I think it is reflective of new therapeutic tools and devices and much more understanding of patients. This is more striking than the mental health figures.

Mr. DENTON. I wish you could make a chart with the mental health figures.

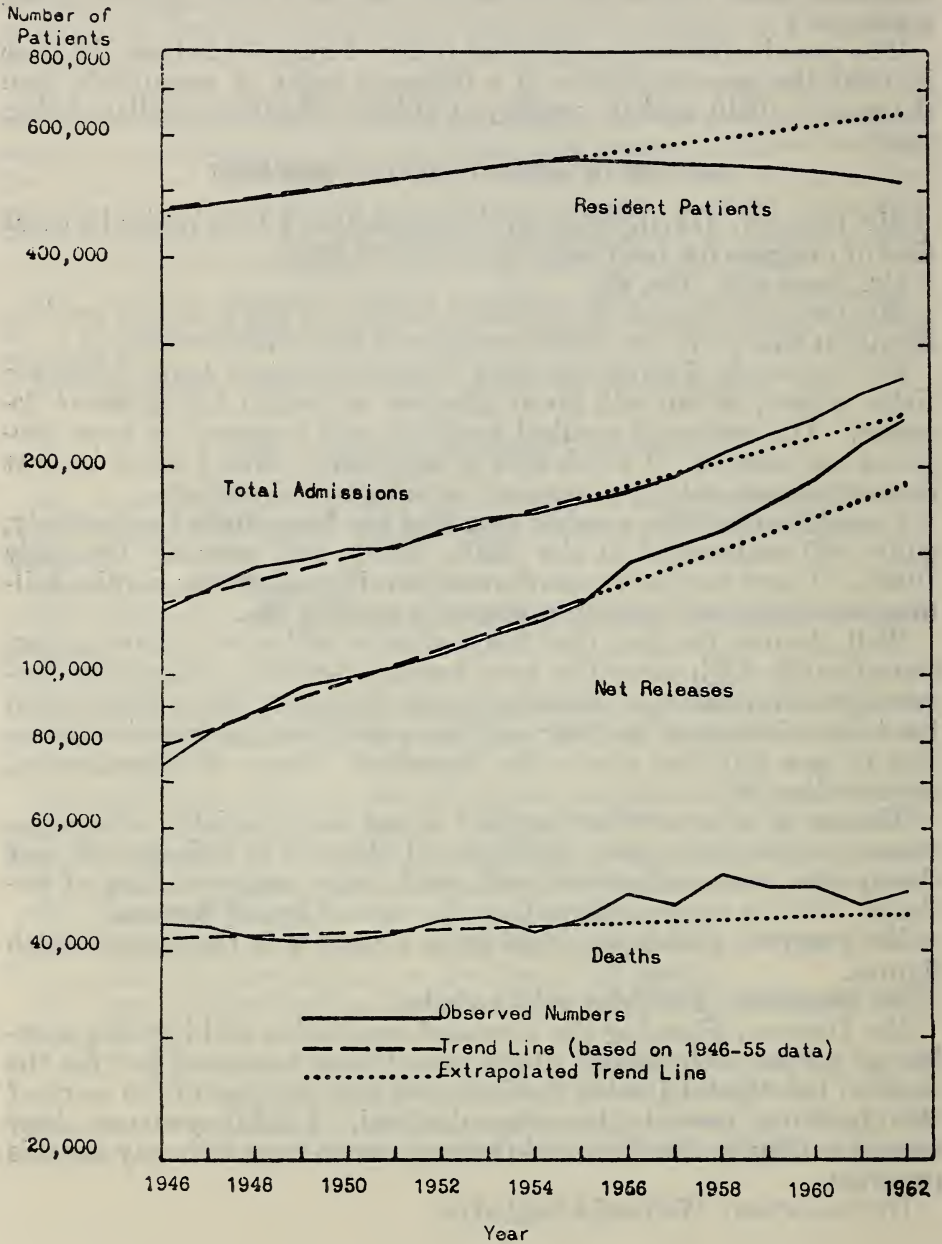
Dr. SHANNON. Dr. Felix will be glad to.

Mr. DENTON. Showing the increased population and how the number of people with mental illness would have increased but for the work of the Mental Health Institute and how, because of the work of this Institute, mental illness has declined. I think you can show enough saving by the State and Government to more than pay for this program.

Dr. SHANNON. We would be glad to.

(The chart follows:)

NUMBER OF RESIDENT PATIENTS, TOTAL ADMISSIONS, NET RELEASES, AND DEATHS, AND EXTRAPOLATED TREND LINES (BASED ON THE YEARS 1946-1955), PUBLIC MENTAL HOSPITALS, UNITED STATES, 1946-62



Source: Data collected in annual census of patients in mental institutions, National Institute of Mental Health.

Had the 1946-55 trend in the resident patient population continued, there would have been almost 650,000 resident patients by the end of 1962. However, the resident patient population has declined since 1955 at an average rate of 1.1 percent per year. The observed resident patient population at the end of 1962 was only 515,948, as compared with 650,000, a drop of 134,052. This has resulted in a substantial accumulated saving in maintenance costs during the 7-year period 1956-62, which is estimated conservatively to be \$700 million.

Mr. DENTON. Those improvements were made very largely by grants from the NIH.

Dr. SHANNON. I think most of the improvements from cardiovascular disease are also.

Mr. DENTON. That is easy to point out, because the money the Government spends taking care of veterans and States spend for mental institutions is so large, and you can document it much easier than someplace else. The big thing is that the improvement is the result of research that was very largely financed by grants made by NIH.

Dr. SHANNON. I think even more so than any other field of science, the totality of the research is supported by NIH.

Mr. DENTON. I remember we figured out in 1 year the savings on that was tremendous.

Dr. SHANNON. Yes, sir.

GRANTS REVIEW PERSONNEL

Mr. DENTON. Coming to the last chart, I just want to ask you who these people are.

You have the Advisory Council. In the case of a cancer grant, are they specialists in cancer?

Dr. SHANNON. The application for a grant would come before the National Advisory Cancer Council.

Mr. DENTON. Those are eminent cancer specialists who are not with the Government?

Dr. SHANNON. That is correct.

Mr. DENTON. Do they get paid for that?

Dr. SHANNON. They receive \$50 a day and expenses.

Mr. DENTON. Now, the people who make up the groups of the advisory councils and study sections are personnel of your department?

Dr. SHANNON. No, sir. The personnel also are for the most part non-Federal scientists.

Mr. DENTON. Oh, they are?

Dr. SHANNON. These are professors, associate professors.

Mr. DENTON. Who are in the Division of Research Grants? That is a Federal operation.

Dr. SHANNON. Yes, sir. They perform the staff functions; they develop the facts upon which advice is given. They are not members of the advisory committees or study groups.

MEMBERSHIP OF ADVISORY COUNCILS

Mr. FOGARTY. Dr. Shannon, questions like those asked by Mr. Denton, regarding your councils, are asked quite frequently. I think it would be a good idea to place the names and titles of all the members in the record.

(The listing referred to follows:)

NATIONAL ADVISORY HEALTH COUNCIL

- Dr. L. V. Berkner (65), president, Graduate Research Center of the Southwest, Dallas, Tex.
 Dr. Michael E. DeBakey (65), Baylor University College of Medicine, Texas Medical Center, Houston, Tex.
 Dr. Edward W. Dempsey (65), dean, School of Medicine, Washington University, St. Louis, Mo.
 Dr. James P. Dixon (64), president, Antioch College, Yellow Springs, Ohio.
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November 1, 1962.

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 Dr. Robert I. McClaughry, director, Educational Services, Department of Medicine and Surgery, Veterans' Administration, Washington 25, D.C.
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 Mrs. Helen L. Curry (1963), 1618 West Sixth Street, Topeka, Kans.
 Dr. Robert J. Glaser (1963), vice president for medical affairs, University of Colorado, 4200 East Ninth Avenue, Denver, Colo.
 Dr. David R. Goddard (1966), provost, University of Pennsylvania, Philadelphia, Pa.
 Dr. Harry F. Harlow (1963), professor of psychology, University of Wisconsin, Madison, Wis.

- Dr. Maxwell E. Lapham (1963), dean of medicine, Tulane University, 1430 Tulane Avenue, New Orleans, La.
 Dr. Raymond J. Nagel (1963), dean, College of Dentistry, New York University, 421 First Avenue, New York, N.Y.
 Ben Taub (1963), executive director, J. N. Taub & Sons, 909 Franklin Avenue, Houston, Tex.
 Dr. W. T. S. Thorp (1963), dean, College of Veterinary Medicine, University of Minnesota, St. Paul, Minn.
 Dr. George A. Wolf, Jr. (1963), executive director and vice president for medical and dental affairs, Tufts New England Medical Center, Boston, Mass.

EX OFFICIO MEMBERS

Dr. Howard E. Page, National Science Foundation, Washington, D.C.

Alternate

Dr. Harve Carlson, National Science Foundation, Washington, D.C.
 Dr. Luther L. Terry (chairman), Surgeon General, Public Health Service, Washington, D.C.

Mr. FOGARTY. Mr. Lesinski?

Mr. LESINSKI. First of all, doctor, on your chart [chart 8] showing the categorical institutions——

Dr. SHANNON. Yes.

Mr. LESINSKI (continuing). The second last line, dental, that is supposed to be 1 million or 10 million?

Dr. SHANNON. One million, sir.

Mr. LESINSKI. The reason why I asked is the comparison in size with the one above, the allergy——

Dr. SHANNON. Wait a minute. That 1 million is wrong sir; that should be 10 million.

Mr. LESINSKI. That is what I thought. That is why I brought the point up.

Dr. SHANNON. It says 1 million but I think the dots in the chart were in the way there.

ADMINISTRATIVE CONTROL OF GRANTS

Mr. LESINSKI. First of all, before we start, I want to say this: I am not opposed to your program as such, per se. I think we all recognize the valuable work you are doing. But there is a matter of fiscal responsibility. I may sound like a Republican right now, but I am an American first. I recognize the need of the aspirations, the research, and so forth. On the other hand I recognize the obligation to the people.

In talking to some of the scientists working on Federal grants from NIH, they claim that they are constantly being watched and that it is not true research. This is one of the complaints I have been getting.

Dr. SHANNON. They are constantly what, sir?

Mr. LESINSKI. Being watched, it is not true scientific research.

Dr. TERRY. These are scientists on the outside?

Mr. LESINSKI. Yes, under grants from the Federal Government.

Dr. SHANNON. Well, Mr. Lesinski, I think this is a comment that we have heard for the first time during the past 18 months and, may I say without being critical of Mr. Fountain and his committee——

Mr. LESINSKI. I did not get it from him.

Dr. SHANNON. I know, but I want to bring this up, because it is part of the problem—he feels, and I think rightly so, that we must interject more administrative controls than had been characteristic of the

program during its earlier phases. But where we do not agree is the character of the controls.

Now, at this point in time, we are being more restrictive of our own grantees, the freedom of opportunity they have, the freedom to transfer money from one budget category to another, the freedom to use funds for the purchase of equipment without prior and specific clearance, the extent to which they retain the substance of their research within the projected scope of their application which has been acted upon.

We hope that as time progresses the limitation which we are imposing on the scientist today can be decentralized for judgment within the environment of the institution where the work is being done, rather than by ourselves in Bethesda. Because we are convinced that we are not in a position to make certain of these judgments.

But we felt that at this point in time we had to comply with some of the direct wishes of Mr. Fountain's committee in exercising certain controls in anticipation of later conditions where local control would be much more possible and advisable than it is now.

I am convinced our scientists in universities over the years have conducted themselves with high integrity.

I don't think funds were generally misused, but sir, we did not have a visual documentation of the sequence of the events and the conditions which lead to program modification, the decision to change budget categories and the like. Sir, we can assure you that misuse of funds was not characteristic of the program.

Mr. LESINSKI. You say the University of Michigan began with—you say the University of Michigan has 239 grants?

Dr. SHANNON. Yes, sir.

MULTIPLICITY OF CANCER GRANTS

Mr. LESINSKI. How many cancer grants do they have? Can you give us that?

Dr. SHANNON. Twenty-nine grants, \$545,000.

Mr. LESINSKI. Twenty-nine?

Dr. SHANNON. Yes, sir.

Mr. LESINSKI. All right. That is exactly the point Dr. Terry and I discussed the other day. The difficulty is you have 29 separate grants at the University of Michigan for cancer. Again, I have to agree with the argument that there are different types of cancer. I am not arguing that question. But would it not be better if you had say, 20 scientists, even 29 scientists in the University of Michigan with \$20,000 whatever it may be, working under one head, and correlating their efforts?

Dr. SHANNON. Well, could I comment on that, I will answer that question but I would like to make a comment first. In some areas this would be advisable, in some areas this actually takes place.

There is within the structure of NIH support in the University of Michigan, as with all other medical schools, the so-called undergraduate teaching grant, some \$25,000 a year. That is a fluid grant to the University of Michigan for such coordination of cancer activities as can make more effective the information available for teaching purposes. In general, this provides for the setting up of a professor with minor assistants.

Now, in some places, this man actually is the focal point for an advisory committee to the institution that relates to the overall development of activity in this area.

We would be very glad to work with an institution providing it would set up such a technique, but I would point out that in the overall, this would not completely resolve the problem, because some of these people are in the university, others are in the school of agriculture, others are in the school of medicine. We could reduce the number of grants from 29 to some much smaller number, but this would require a somewhat different authorization than we have at the present time; it would require a fairly broad redefinition of the responsibility of the University of Michigan, and would in fact require that they set up a scientific organization in parallel with their instructional staff in order to interact with us on a categorical basis.

Now, it is a question which is wiser, to carry large numbers of grants without direct interference with the university structure or to carry a smaller number of grants and insist that the university modify its way of doing business so that we can have what would appear to be a more ordered program?

Now, substantively, sir, I do not believe this would affect the substance of the program. Because if one goes down the list here, and I would like to read it here, I will go from the top down: Genetics of tetrahyemena; effects of cancer on the metabolism of the host; antibodies to thyroid cancer; comparative evaluation of chemotherapy of leukemia; midwest cooperative chemotherapy group—they are used as a center to develop cooperative results in this area in related hospitals—potential anticancer agents, the agasteroids; radioisotope localization in neoplasms; sites and reactants participating in cellular transport—in other words, the substance of these individual operations will relate more closely to operations going on in adjacent States, like Wisconsin, than something going on in an adjacent department in the University of Michigan.

While one could present a much more orderly front to the public in such an organized cancer program, I do not think that the individual scientists would modify particularly what they are doing. Nor do I think that the integration that might come from an organization of this sort would catalyze more effective work.

I think that this, again, is more interinstitutional than intrainstitutional in nature and the character of science in these areas, and medicine really in general, defeats the ability, or defeats attempts to try to manage it, if you will.

Now there are areas in cancer that have to be highly managed and I hope that Dr. Endicott will go into these when he testifies tomorrow.

It would be sheer folly to run a cancer chemotherapy program where the decisionmaking process was peripheral in the individual scientist's laboratory. It would be sheer folly to undertake systematic study of the role of viruses in the production of cancer again where these many decentralized decisions are made. It would be sheer folly to make a systematic attempt to develop diagnostic tests where individual scientists were making their own decisions.

So when there is an area that is amenable to planned operation, where one is going to substitute group for individual decision, the Cancer Institute undertakes the type of organization that permits

that, but this still leaves roughly 50 or 60 percent of the total program where the state of knowledge is so primitive, if you will, that we still must depend upon qualitative new ideas that emerge in the mind of the individual scientist and provide him with an opportunity to explore his own ideas.

I am sorry that it is not different, but this is the stage of knowledge today.

EMPIRICAL RESEARCH

I might say, sir, that I participated very effectively in what was probably the most effectively planned medical research program in the United States, and that was the World War II program in malaria. This was a rigidly controlled, rigidly run and highly productive operation. But the stage of knowledge at that time was such as to permit an engineering type of approach, and I think by that engineering approach, we accomplished in 2 or 3 years what otherwise probably never would have been accomplished.

Now we are in a position where the very antimalarials that were prepared in World War II are now showing to be quite ineffective around the world, and we must return to development of new antimalarials.

During that entire period of time when there was this intensive study of antimalarials that resulted in fantastically effective drugs, there was no increase in the basic store of knowledge. So what has to be done now was precisely what was done in 1943 when I was involved; they will go back and establish, as they are in cancer chemotherapy, a very broad screen to examine chemicals that have never been examined before simply in the hope that new chemical types will be found to be effective.

Mr. LESINSKI. In other words, there are two things here, basically, you told me; it is possible to implement a large grant at the universities?

Dr. SHANNON. At the universities; yes, sir.

Mr. LESINSKI. Now, you just told me what sets me back a little bit; every time we find out something new, the bugs resist it and then we have to start all over again. So where are we getting in the ultimate end?

Dr. SHANNON. Well, that is not entirely true, sir.

Mr. LESINSKI. Well, let me carry it on.

Dr. SHANNON. Yes.

Mr. LESINSKI. Because I said it in a few words.

It was said to us the other day, I believe it was for syphilis, that the penicillin is used and syphilis was building up resistance to it. He mentioned malaria; they had found the old methods are not as much value as they thought they were due to the fact the malarial germ developed an immunity to the original methods. That is exactly what I am driving at, the fact you go through all this trouble, spending funds, finding means or ways of doing away with something; then the insect develops an immunity, then you have to start all over again.

Dr. SHANNON. This is correct.

The thing I would point out, in each of these instances, the therapeutic agent or the insecticide or the antimalarial that was developed was developed by a wholly empirical method without any understanding of the underlying biological mechanism it was affecting.

I predict, sir, this will be the story of all chemical therapeutic agents, essentially all, until we obtain a more fundamental understanding of the biologic chemistry of the organism.

Meanwhile the chloraquine has controlled malaria throughout the world for the better part of 20 years. This is a worthwhile accomplishment in itself.

I will point out also this is not causing worldwide malaria at the present time, but resistance has appeared, foci—the writing is on the wall. Come 5 or 10 years from now, the Armed Forces will not have an effective antimalarial unless one takes this warning and develops a substitute for chloraquine in the meanwhile.

So that while I am sorry that what you say is correct, too frequently, particularly in antibiotics or anti-protozoan agents, a resistance very often, on the part one wishes to kill, develops. Nonetheless, this is a reflection of our ignorance, rather than any other thing.

Mr. LESINSKI. In other words, unless you wipe out a disease completely you never have any control and it might recur because of the fact that disease will build up a resistance?

Dr. SHANNON. Well no. Resistance, emergency resistance, does not obtain universally. It does obtain sufficiently often to be a very disturbing thing and I think very few people would hazard a guess that in rapidly growing forms, bacteria, protozoa, and the like, the possibility of developing resistance forms is ever absent, and my own conviction is that until such a time as we can examine the curtailment of growth of the organisms in a much more penetrating and rational way than we do at the present time, this is going to be the story of the antibacteria; antifungi; and antiprotozoan agents.

UNIVERSITY OF MICHIGAN

Mr. LESINSKI. Talking about the University of Michigan, I have very good coordination with them at the present time, and we have had our differences at one time, too, if you think I am going to sit back here and worry about it, I am not. I will be frank with you, Doctor. I don't scare that easy.

Dr. SHANNON. That was not for that purpose.

It was for the purpose that, if you take a listing and take the last column, and see the diversity of the departmental activity which is contained in the field of cancer, then you can get some concept, within a single institution, of the diversity of activity that is necessary or the judgment that is necessary, if we are ever going to find a solution to our problems.

Mr. LESINSKI. The University of Michigan has a number of private holdings. I forget how much it is. It is in the millions of dollars, annually, from the deceased alumni, that were willed to it.

Mr. FOGARTY. Is that State-supported?

Dr. SHANNON. That is State-supported.

Mr. FOGARTY. It costs the State a lot of money to run that university.

Mr. KELLY. May I say, with respect to the table that was prepared on Michigan, that you will recall when the Office of Vocational Rehabilitation was up here, that they gave a statement that described the program that was going on in each of the States represented in the committee, and I thought the committee found it particularly

interesting and an easier way to understand what the program is doing at home. So I called Dr. Shannon's attention to this. Also, you indicated an interest in the question as to how much of these funds were expended by the Federal Government in Washington or for the operations of a Federal staff, and I thought that this helped to show the extent to which these total funds go back to the institutions.

Mr. FOGARTY. I think this is an excellent way of presenting the story.

Mr. LESINSKI. Dr. Shannon, now, this question, I am going to ask you anyway.

Dr. SHANNON. Yes, sir.

EXTENT THAT RESEARCH FUNDS AID UNIVERSITIES

Mr. LESINSKI. Isn't this a back-door method of financing colleges or indirectly financing?

Dr. SHANNON. No, sir. It is not a back-door method of financing colleges. It is a very direct and open method of enriching the staff and enriching the environment in which the educational process takes place. We at no time have denied, as a matter of fact, we stated that our medical education today is better in no small measure because of the staffs that schools can now have, because of the support of science and the profound impact of ongoing science within which medical students are taught. The thrust of your question is completely correct, sir, if you say this has a profound influence on the educational process, and I don't doubt at all there is some spillage of dollars into the educational process, because when one deals with the support of a single function, in a situation where there is intermingling of research, education, and service, it is impossible to completely compartmentalize the end use of any one area.

I would say, on the other hand, that education contributes a great deal to our program, because most tenured positions, tenured physicians and tenured professors, are working on our research grants at no salary cost to us. So that there is an overlap that goes both ways, and I would say we probably benefit more than does the educational process.

Mr. FOGARTY. You don't have back-door spending in the sense that it is money taken from the Treasury without going through the regular appropriation process?

Mr. LESINSKI. No, sir.

Mr. FOGARTY. All of these appropriations are authorized by Congress, and then go through the appropriation process. That has not happened in some other programs. I just brought it up because that is what is usually meant when we refer to back-door spending.

Mr. LESINSKI. I am glad the chairman brought that up. I did not mean it in that respect.

Another point I want to bring up here is the fact that many colleges teach students and they come out taught knowledge in a narrow scope, but not in practical appliance of the science. Therefore, what you are doing here is, while teaching, you are giving them a practical implementation with the study of science, which makes a better or more valuable man out of him.

Dr. SHANNON. We think so, sir; yes, sir.

Mr. LESINSKI. I commend that approach, because I have always said that a college man with a practical knowledge is an asset, whereas a college man without a practical application is narrowminded for he sees only what he was taught.

Mr. Chairman, thank you.

Mr. FOGARTY. Mr. Michel?

Mr. MICHEL. Dr. Shannon, just one question. On the graph, you show sources of medical research funds.

Dr. SHANNON. Yes, sir.

FUTURE FEDERAL SHARE OF MEDICAL RESEARCH SUPPORT

Mr. MICHEL. The proportion, as it is divided between Federal, non-Federal, and industry, and there is no question that there has been an astounding rise in the Federal part of the total from 1957 to 1963.

Do you anticipate that that curve in the next 5 or 10 years, will remain constant, or would there be a leveling off? What do you foresee?

Dr. SHANNON. I wish I had a definite answer, sir, but I would like to point out in all honesty that I think the Federal contribution probably will increase.

I think the extent to which it increases will depend upon a series of factors.

Now, the data refer to all health research. I think that there was broad discussion here about the environmental sciences. I think that research in such areas will expand, and depending upon the reaction of industry, they will be a major source of dollars, because if industry does what I would hope, in this situation, the Federal expenditure would be small as compared with the private.

Now, in the more conventional type of research—the type of research that this committee has dealt with at the present time, I think there we see another trend that is difficult to predict. Some of the States—New York State and California are two leaders in this area—they are really putting up their own budgeted dollars, substantial amounts of dollars, into research.

New York City is putting, of its own money, something like \$10 million in medical sciences. So that I think what happens in the next 10 years depends upon whether these things are beginning trends or not, and I think, in part, this depends upon a whole host of things, such as tax structure, and I am lost when I get into it.

There is a variety of factors that are going to determine project giving—State versus Federal share, State versus initial share of the tax dollar; and then we have the State spending and we have municipal spending. These are so far beyond our control, the only thing that I can be certain of, I take it that there will be more, there will be better health; and there will be a better environment. It is my technical judgment this can only come with the acquisition of new dollars and its rate of application which means more research and more technical assistance. The total expenditure is going to be substantially larger than it is.

That is as honest as I can be.

Mr. MICHEL. Thank you, Doctor.

Mr. FOGARTY. Doctor, is there anything else you want to say about these charts before we get into other areas?

Dr. SHANNON. No, sir. I would like to say, Mr. Chairman, I am very glad that you have given me the opportunity to put some of these generalities into the record, because it does help.

Mr. FOGARTY. I think the charts were very helpful in presenting some of this overall information.

Dr. Shannon, there is hardly a family in the country that is not affected by heart, cancer, mental, or one of the neurological diseases that we are spending funds on.

Dr. SHANNON. I would say that the family is exceptional that doesn't have an example of each of the categories.

Mr. FOGARTY. Every poll that has been taken, that I have seen, as to whether or not the people agree with these expenditures for research has shown there were 70, 75, or 80 percent in favor of it.

GRANT FIGURES WITHIN SELECTED STATES

Mr. LESINSKI. Mr. Chairman, there is one question: Are all these from the State of Michigan?

Dr. SHANNON. Yes, sir. We passed out five groups of tables, and they had not all been taken off the machine when I left. What I asked for was a breakdown of the grants; that is, research grants by State, of the five States represented here. A breakdown of the training grants by State, and then a summary of research fellowships and such other grants as can be dealt with in summary form, and what we will do, sir, what we would like, as I told Mr. Fogarty before the hearing started, we expected to come up tomorrow afternoon so we don't have these tied together by State—otherwise, it would be easier for you to look at. So these came right off the machine.

Dr. TERRY. Mr. Chairman, while we were talking about the question of Federal participation and Federal support, I thought a matter of interest to be called to the committee's attention, is a recent figure compiled by the National Science Foundation on the expenditures for separately budgeted research and development in colleges and universities, by the field of science, and the source of support for the fiscal year 1958, and pointing out that in the fields of science the Federal percentage participation of the total, for instance in engineering was 85 percent, in the physical sciences 90 percent, in the life sciences 50 percent, and in the social sciences 48 percent.

So that I think that this points out very clearly how there is a multiplicity of support in the life and social sciences and where the Federal degree of participation is considerably less than, for instance, in engineering and the physical sciences.

Mr. FOGARTY. Is there anything else you want to say about the charts before we go on?

Dr. SHANNON. No, sir.

ADMINISTRATION OF GRANT PROGRAMS

Mr. FOGARTY. I think we ought to go into this question of grant management rather thoroughly. Congressman Fountain's Intergovernmental Relations Subcommittee of the House Committee on Government Operations has been looking into your administration of

grant programs and released a summary report last June, which contained a number of criticisms and recommendations.

Now I think it might be fruitful to discuss, generally, some of the committee's findings.

Dr. SHANNON. Mr. Chairman, I agree heartily. The subject is of such importance, as I indicated to Mr. Lesinski, that we prepared a special report to your committee on the steps we have already taken to strengthen the administration of our grant programs.

I would be glad to make that report available to you immediately, but I think it might be worth while to explore some of the matters contained in the report at the same time.

First, I would like to make clear that I believe that Congressman Fountain's subcommittee has performed an important service in pointing out some of our administrative gaps. Our special report, that I referred to earlier, describes some of the efforts, and these are quite intense, that we are devoting to strengthening our administration, our administrative procedures, in the grant area.

I believe you will be gratified in that it does outline some important strides that have been taken toward improving the management of these programs. As you know, sir, we have had considerable growth and success in managing the growth itself. It is not unaccompanied by administrative problems in adapting program guidelines and mechanisms to a growing activity.

I don't wish to minimize these problems, but it seems fair to say that the mistakes were bound to occur in the course of the developments that characterized this dynamic program—that characterized our programs over the past years.

I would say that you will find mistakes in any fast growing enterprise. The important thing at the present time is, I believe, that we are moving as rapidly as we can to both close policy gaps and strengthen internal management to cope with the program changes that will emerge.

PRODUCTIVITY OF RESEARCH

I would like to emphasize also—and this is emphasized by Mr. Lesinski's comment—that we must not lose sight of the fact that our period of rapid growth has been accompanied by an extremely productive period in medical research. We should keep this in proper perspective as we discuss our administrative problems. Administrative mistakes are frequently the price we pay for achieving significant program progress.

One must continually stress the question of how productive our operations have been in terms of research results. This is the final test of our enterprise. Your committee emphasized this point a number of times, and I think a lesson can be drawn from our experience to date that, while we are moving toward improved management, we must guard against overly detailed controls on the scientist's ability to use the funds in the fashion that he, himself, thinks will best accomplish productive results.

In the final analysis, a research grant is a bet that is made on the productivity of the individual scientist, his brain, his research capabilities, and his environment after an assessment of the resources available to him.

ACCOUNTABILITY VERSUS FREEDOM OF INQUIRY

Thus, in this relationship, we must provide for accountability on the one hand, and terms and conditions of support on the other that give the individual the actual opportunity to make the contribution that we had in mind in making the grant available to him.

It has been our experience, it has been the experience of every granting agency in this country in recent history, that fostering this freedom of inquiry is the most important characteristics that must be preserved, and it is in reality the prime consideration for assuring the maximum yield on the taxpayer's investment in medical research. This may lead to some administrative errors along the way, but I submit that such freedom is a primary prerequisite for a truly effective and economical operation.

Now, I don't feel, sir, that these two objectives are necessarily in conflict. We must always try to minimize administrative error. In other words, what we must seek is accountability on the one hand, and academic freedom or freedom of research opportunity on the other.

This is an extraordinarily complex thing, sir. I think we have made great progress in pulling these two things together, and if we have failed in part, it will not be because of lack of good people on the job, trying very hard.

EFFECT OF RAPID GROWTH

Mr. FOGARTY. To what degree has the rapid growth in both the size and complexity of your programs contributed to your administrative difficulties?

Dr. SHANNON. Well, as I indicated, I think that the conduct of any program presents administrative problems, but I would be the first one to agree that in a program which in over a decade and a half has increased some twentyfold, that this in itself has precipitated much of our difficulty. In more concrete terms, in a 10-year period the number of our grants has increased from some 2,000 to some 14,000. In addition to the simple number of regular grants over this same period of time, it has been necessary, in order to take advantage of the many types of opportunity available through medical research to add some broad program grants that are less restrictive than the individual project grants, to make use of Federal funds in the establishment of an array of clinical resource centers; to make available special grants in the area of computer and bioengineering technology; to initiate a program for the general support of research and training within institutions which have a heavy involvement in the biological sciences; and to extend, in a small measure, our grants abroad, in order to take advantage of certain skills that are available in the international field, but are in quite scarce supply in the domestic market.

I believe that these data, mainly the quantitative data, the dollars, the number of grants, and the increased complexity of the program, are indicative, on the one hand, of administrative problems encountered and on the other, are the reflection of the tremendous development, the tremendous expansion of the medical research effort of the Nation.

I would say that again, the accomplishments that have been obtained through this effort, have been worthwhile, because in the final analysis this is the judgment that has to be made. However, I think it is impossible to grow at such a rate and take on new programs, without experiencing a number of administrative difficulties which necessarily accompany such basic changes. However, I emphatically believe that such program growth has made a tremendous contribution to the welfare of the Nation. I think the committee will obtain ample evidence of this during the course of the hearings.

Our problem continues to be to adjust to these changes while, at the same time, maintaining the basic values and concepts and relationships that have produced such fruitful results.

ADMINISTRATIVE IMPROVEMENTS

Mr. FOGARTY. I think it would be worthwhile if you would generally identify some of the recent steps you have taken to improve the administration of the grant program.

Dr. SHANNON. Well, sir, there are a number of generally broad categories. If I can organize my thoughts for a moment.

CONTROL OF GRANTEES USE OF FUNDS

I would say, first, that additional steps have been taken to make certain that the grantees spend the funds awarded to them for the purposes for which the grant was made.

Now contained in that simple statement on the one hand is a situation fraught with hazard for the future of American science and, on the other hand, it is a sound administrative statement. This is perhaps the key issue.

A grant, in our view, is a conditional gift from the Federal Government to the institution in support of an individual, whereby the institution and the Federal Government join in common purpose. The common purpose is to resolve certain broad definable scientific issues. As long as the scientist retains his interest in furthering research for the solution of the basic objective he has set forth, we would say that his work is contained within the project he has submitted to us for support. On the other hand, within this basic objective he should be permitted to change his methodology or approach as the course and result of his research dictate.

So that on the one hand one can be strictly accountable for maintaining activity within a defined project and at the same time provide to the scientists the necessary measure of freedom.

Now on the other hand where a scientist receives a grant in the area of cancer and, through some unforeseen development, elects to modify his field and search out completely different research objectives, then we are saying under such circumstances the grant would not have a flexibility that would permit such a movement. He would have to come to us again and ask approval for such a basic change in the direction of his research.

I think that we have taken steps that will make clear the need for the individual to be conscious that there is some limitation on this freedom, but this limitation will not be burdensome unless there is a fairly complete change in the field.

RESPONSIBILITIES OF GRANTEE INSTITUTIONS

I think the second broad category is that we have made quite clear to grantee institutions what responsibility they assume when they accept grant funds, and I think that we are in the process of making certain that the institutions have the capability of discharging this responsibility.

Now, again, this is a broad statement that requires some modification. We have been in continuous contact with our associations of medical schools who receive approximately 50 percent of our research funds, and who are closely associated with teaching hospitals, large hospitals, and hospital complexes that receive up to an additional 25 percent of our funds.

We have had formal centralized meetings with their administrative staff, followed by two cycles of regional meetings, first with the deans of the medical schools and, within the past 2 weeks, we have also gone in the field to hit into the universities in the arts and sciences environment. These latter accept roughly 25 percent of our funds.

These are straightforward administrative sessions, where we have outlined the problems we face; we outlined the administrative controls we wish to institute. We have had discussions as to how these controls can be exercised within their own environment and the type of information that we will require as documented information of compliance with controls.

We pointed out that the present grant programs will require a type of administrative decision that must be made in Bethesda until such time as the grantee institutions can show that they have the apparatus and the mechanics with which to reach these decisions locally. We have indicated that when they feel they are ready to discuss the suitability of the administrative mechanism they develop, we will be glad to sit down with them and determine a sharpening of this responsibility. I wish to make it clear that this will be done within the framework of established policy and with constructive assistance from our staff.

I might say this has been a fantastic effort. It has involved the traveling of a substantial number of our top staff throughout the country. It has involved the travel of a substantial number of deans, vice presidents in charge of medical institutes, professors and the like, and I can report to you that the institutions themselves are not resentful of the conditions we impose. They are fully cognizant of the need for the development of broader administrative controls, and we are well on the way toward their development.

UNIFORM GRANT REGULATIONS

I think in the third broad area that we have now set up a complete and very orderly policy for developing and issuing grant regulations. I would like to expand on this, if I may, Mr. Chairman. You have been with this committee since the beginning of the grant program. You recall in 1946 I think the total grant activity was something like \$350,000, and this constituted a simple extension of the grants that had been supported by the Office of Scientific Research and Development.

In the early days, every grant was an individual action. Dr. Dyer, as Director of the National Institutes of Health, was well aware of the conditions and circumstances of the grant, and there was not need for a highly regularized program.

Now as the years passed, and as the grant programs became more complex we have established within each institute what I think to be quite adequate administrative devices; but because each institute is somewhat different from the other, the rules and regulations within each institute were not wholly identical with that of one of the adjacent institutes.

Now this is something that we could live with, but this is something that is very confusing to the schools, because as far as the schools are concerned they are basically dealing with NIH as a single entity.

Because they are basically dealing with all of NIH, they face the possibility of six or seven—I am exaggerating a little—different rules and regulations, depending on which appropriation their support funds come from.

Now, we think that there has been some loss to the individual institutes in the total regularization of the grant program because there is very little permitted in the way of variation, but we think the gain far outbalances the loss. There is a loss of freedom on the part of the NIH institute, but the gain in understanding on the part of the university is immeasurably greater and I think on balance, we are way ahead.

I might say that regulations covering our research grants will shortly be published in the Federal Register and will be as binding as any other rule or regulation so published.

Now, we have talked a little about strengthening the understanding of the institution: we have talked a little bit about the formalization of procedures.

INTERNAL ORGANIZATIONAL CHANGES

In order to make these things work, a fourth broad area has been our efforts to strengthen our internal organization and to increase the administrative staffing of our grants program. We have done this in both the general division of research grants, and we have done it within the individual institute appropriations.

I might say that one of the major staff moves here was the establishment within Dr. Terry's office of a Grant Policy Office, and Dr. Allen, who has been with NIH since the beginning of the grant program, has become Dr. Terry's special assistant to head that Office.

We in NIH have accepted "single manager" responsibility in the Division of Research Grants for providing central grants management operating services for all the Public Health Service, and we will continue to service the grant programs of the Bureau of State Services, as well as the National Institutes of Health.

We have greatly increased our concentration on grants management within the Institutes, and we have also defined a broader and clearer program analytical function within the Institutes so that more attention is given to specific program development. Finally, as part of the strengthening of this administrative apparatus, we have, I believe, more sharply defined the dividing line in program development between the advisory function of the non-Federal scientist and the

administrative responsibility of the executive agency that has the responsibility for program execution.

Now, Mr. Fogarty, these are, in general, the areas where we have taken positive and, I think, very definitive action.

Mr. FOGARTY. Now, could you illustrate more specifically, some of the actions you have taken under these general approaches?

Dr. SHANNON. Well, if I could go into some detail.

Mr. FOGARTY. I think we have to.

Dr. SHANNON. Yes, sir.

Let me develop a little bit more thoroughly the organizational changes that, in the final analysis, will determine the extent to which policies can be evolved in a rational way.

First, let me say that we had a number of management improvements underway prior to the Fountain committee hearings—among them the development of a manual of research grants policies and procedures.

INTERBUREAU DIRECTING COMMITTEE

Secondly, after the last Fountain committee hearing, after discussion with the participating PHS Bureaus, Dr. Terry appointed what was called an interbureau directing committee, for purposes of inquiring into grants policies and procedures, and grants management.

The chairman of that committee was Dr. David Price, who you know, at that time, was Deputy Director of NIH. Dr. Price was the obvious choice, because he had been associated with the grant process in one form or another, since it was originally established. Dr. Price now, as you know, is Deputy Surgeon General.

Dr. TERRY. I think it is important to point out that Dr. Price, in addition to his NIH grants experience, had considerable experience in our Bureau of State Services, in dealing with the grant process there, as Chief of that Bureau at one time. Also, Dr. Price has been Deputy Chief of our Bureau of Medical Services, so he is one of the people who has had a great deal of experience in all of the broad operating responsibilities of the Public Health Service.

Dr. SHANNON. I might add, further—and this is to further describe Dr. Price's broad experience—he had been one of the senior advisers to the Polio Foundation, which had run one of the more sophisticated grant programs in the private sector. This directing committee, under Dr. Price's leadership, was composed of senior personnel from all the Bureaus, including NIH, and they were given the task of studying the whole grants administration, in order to make recommendations, not only to NIH but to the entire service. They looked particularly into how some of the soft areas could be solidified, how some of the fuzzy areas clarified, and how some of the undefined areas could be fairly rigidly defined.

This study was staffed by full-time, topflight staff people. It took the better part of 3 months. It was completed in June 1962. The report was sent to Dr. Terry, and this report was discussed at some length with the National Advisory Health Council, together with representatives from the other councils. This was particularly important because the implementation of the things that were contained within the report would have a fairly profound effect on many actions that the councils are asked to advise on.

In our own bureau, the National Institutes of Health, we set up a small working group who were responsible for developing the implementation of the directing committee's report. The general report did not spell out in detail the specific actions that had to be taken, and our problem was to develop the specifics that would apply to the NIH environment.

RESEARCH GRANTS MANUAL

One of the first steps we took—to which I have already alluded—was the development of a research grants manual that defined the procedures and the policies applying to the research grant operation. This manual was released to grantee institutions last December.

It was this manual that was the focus around which our meetings with the deans and university folk were undertaken over the past few months.

This document further contains a fairly clear preface that spells out as clearly as we could write it, the role and responsibility of the grantee institutions and the role and responsibility of the Federal agency in administering PHS grant programs. This document emphasizes what I indicated before, that we view a grant as being a mutual joining of interests on the part of the grantor and the grantee institution in the pursuit of a common objective.

DISTINCTION BETWEEN WORK DONE UNDER CONTRACT AND GRANT

In this preface to the manual, we make the point that a grant is in quite distinct contrast to a contract, wherein the Government completely directs the program, lays down the specific terms and conditions, and in fact, requires a very specific end product. I might say that this clear-cut differentiation which we regard with such importance at the NIH is not uniformly held in other agencies—in great part for historical reasons—but we feel that, as programs become even more complex, the need specifically to clearly differentiate between the grant and the contract is going to become abundantly clear.

We think on a conceptual level they are different—the grant is geared to support a research project initiated outside the Government, the contract to a project initiated and directed by us. We feel the legal background is different. We feel that the freedoms that can be granted under one cannot really be granted under the other. We believe it is important in such complex programs as ours, to keep these two basic mechanisms separate and distinct and to build up a frame of reference which clearly differentiates between their use.

GRANTEE MUST ACT IN PUBLIC INTEREST

A basic thing in a grant in our concept, and one which our discussions reveal has complete acceptance by the universities, is that in the grantee relationship the grantee assumes with the granting agency an obligation to act in the public interest.

The bulk of the institutions we are dealing with have that concept as the fundamental guide for their total operation. This is not a new concept to them. It is a relationship of trust which imposes upon the grantee certain responsibilities and these responsibilities are shared with the Government in the administration of the program.

On the other hand, this relationship also involves certain obligations on the part of the Federal Government not to interfere with the discrete mechanisms within the institution that are specifically designed to carry out its own responsibility. We may at times disagree with them in the interpretation of what their responsibility is, but we should not tell them how to discharge it as long as we are assured that, by whatever means they do discharge their responsibility, public funds are adequately protected.

I think that we are headed in the right direction, one that will permit the establishment of mechanisms that will provide for decisions being made within the environment of the scientists by responsible grantee institution officials. I would like to quote an example.

LIMITATIONS ON EQUIPMENT PURCHASED BY GRANTEES

At the present time our regulations impose rather specific limitations on the purchase of equipment. It is possible rather arbitrarily to select a dollar limitation on that equipment which can be bought without special permission, whether it is \$500, \$1,000, \$5,000, or \$10,000. We thought the breaking point between a large piece of equipment and a small piece of equipment would probably run about \$1,000. If an individual does not have an equipment item identified in his research grant and the piece of equipment costs more than \$1,000, he must receive specific permission both from his own institution and from the PHS before he can purchase it. In other words, he can buy something that costs \$995 without permission. He cannot buy something that costs \$1,005 without permission. If you have a rule, it has to be that way.

So, after receiving the approval of his own responsible administrative official, the investigator writes in to a scientist who is in an administrative position at NIH and he says the complexion of the research has changed. It has become abundantly clear that there is sedimentation of some biological material. This must be done at low temperature. It cannot be done at room temperature. He must have a refrigerated centrifuge. The refrigerated centrifuge costs about \$1,200.

So our scientist takes the letter, reviews the original research grant application, and then has to make a judgment at his desk in Bethesda as to whether this request is reasonable.

We think this is the type of judgment which should be made locally; made not by the scientist, alone, but by the scientist in association with responsible scientists and administrators in his own institution so that a sounder judgment can be made. We don't think our scientists in Bethesda have enough of the information that will permit these judgments.

I picked a simple illustration where the judgment is fairly discrete, but with programs as large and as complex as ours, we should decentralize this responsibility and do it in a fashion whereby we are assured that considerations that go into these judgments are both sound and advisable.

The problem is not to assure compliance with our regulation that if the item costs more than \$1,000, they ask our permission. This is not a problem. The problem is to make certain the initial decision is a responsible one: that is, whether he should or should not apply the

instrument at all. This judgment is made best within the scientist's own scientific environment. It is not a decision that can be made in Washington.

INSTITUTIONAL CONTROL OF RESEARCHERS

So that, I think our basic approach should be to set forth a clear set of public policies, of standards that must be observed by the institution holding the grant funds.

I think that we have to assure ourselves—and this we are in the process of doing—that in fact the institution we deal with establishes adequate controls to comply with the policies, and, on a continuing basis, we must make periodic site visits to assure that these controls are operative. We must also continue and strengthen our program of postaudit to detect inconsistencies and errors.

This is going to involve work on our part with a great many individual institutions, but I think eventually this will lead to the delegation to them of quite broad responsibilities. In the meantime, I will emphasize that, as I said to Mr. Lesinski earlier, we may have to be guilty of looking over the scientists' shoulder until we can be assured that grantee institutions can assume these delegated responsibilities. Over the long run, however, these conditions must be modified and individual judgments must be made outside of Washington if we are to have a productive scientific effort in our Nation.

GRANT AND CONTRACT DIFFERENCES

Dr. TERRY. Mr. Chairman, Dr. Shannon referred to the difference between research grants and research contracts. I think in this respect, I would like—if it is agreeable to you—to have him explain just one other step that we have taken in relation to the difference in handling contracts and grants. I think this is another important move that we have taken with respect to profitmaking institutions.

Dr. SHANNON. Well, I will approach it in even a little bit broader fashion.

In the process of reanalyzing the terms of our grants, we have attempted to isolate all actions that we feel can be more suitably done by contract, either because of the nature of the job or because of the relationship that is involved. Dr. Terry made specific reference to profitmaking institutions. We feel that a profitmaking organization cannot, in a real sense of the word, undertake the same kind of an arrangement as an educational institution, for example, because the primary purpose of the organization is to make a profit. We felt, therefore, that grants should not be made to profitmaking organizations. We extended that concept further and said that since certain types of work cannot logically be supported by contracts, we will not support work within profitmaking organizations unless there is a determination by our own staff of the program need for the research.

Now, in doing this, we have cut ourselves off to some extent from a segment of industrial science but we felt, on balance, we gained more. So we don't make grants to profitmaking organizations; nor do we sponsor contracts, except on the initiative of our own staff. Incidentally, it was a specific grant to a profitmaking organization about which the Fountain committee was particularly critical.

NEED FOR DECENTRALIZED ADMINISTRATION

Mr. FOGARTY. Doctor, you have referred to the difficulty of handling grant administration from one central point in Washington. In previous appearances before this committee, you have discussed with us your plans to decentralize some of your staff. How is this coming along?

Dr. SHANNON. Well, Mr. Fogarty, I wish I could report that it is coming along more rapidly than it actually is. I can give you a factual account of where we are.

We are still convinced that decentralization of some of our activities is necessary. We think we will have the first experimental setup in the field this summer. We plan to negotiate with a number of institutions in the Boston area to accept a study group up there. This will be tantamount to a university based center, located in a highly populous area that has a high concentration of research and research development activity.

The first pilot installation will have elements of NIH; it will have elements of Environmental Health and of Community Health. And we will attempt, in a period of some 4 or 5 months, to determine how far we can locate our administrative processes on a geographically dispersed basis. If this Boston pilot installation proves successful and we find that we can decentralize in a highly effective, efficient manner, then we will move into other comparable areas. Some that suggest themselves are the San Francisco, Los Angeles, Chicago, New York, Philadelphia, and Baltimore areas.

This would parallel the other development we have just discussed. If we decentralize a good deal of the individual grantmaking decision to the grantee institutions, then I think we have to parallel that with a decentralization of our administrative apparatus to sites adjacent to these institutions. This will provide them with the type of on-the-scene assistance which will permit them to operate effectively in the field of grants management. I look on these as complementing actions.

Mr. FOGARTY. You described some of the specific actions you have taken to strengthen your administrative mechanism. Are there further examples that should be noted?

UNIFORM GRANT REGULATIONS

Dr. SHANNON. I mentioned earlier and would make special note of the preparation of formal regulations on research project grants which will very shortly appear in the Federal Register as one example. These will contain very specific policies that have been developed on a number of controversial issues where we had to make definite administrative decisions.

Our research grants manual contains some very important new statements we have developed in such areas as salaries charged to grants; the handling of travel; the handling of equipment; charges for alterations and renovations; and a whole host of administrative actions and responsibilities that up to the present time, have been unclear.

There are the types of things we have attempted to make clear in these policy statements. We have, for example, stated unequivocally that there shall be no salary differential which results from the fact that a scientist is paid from PHS rather than grantee institution funds. Furthermore, grant funds may not be used for the purchase of any single unit or piece of equipment costing in excess of \$1,000 which has not received prior PHS approval, and grant funds may not be used to equip or furnish offices, reception rooms, conference rooms, or similar space, unless we specifically approve such use of the funds.

We are only approving funds for travel in the grant application if the travel is essential to the successful prosecution of the research being supported, and no funds may be transferred from other budget categories for use in travel unless we specifically approve this transfer. This rule is also applicable to transfer of funds from other categories into alterations and renovations; patient costs; publication of books and pamphlets; fixed equipment; and movable equipment costing more than \$1,000.

IMPROVEMENTS IN GRANT PROGRAMS

We have broadly strengthened our procedures for reviewing grant applications during their initial review by study sections and other preliminary review panels. We are revising the application form to obtain more detailed information. I might say more detailed information that can be picked off by electronic aids, so that we have a more rapid and efficient analysis. We have also made more uniform and formal the information provided to advisory councils out of the initial review process and formalized our reports of onsite visits to grantees.

Very pertinent to the problem of running a grants management shop, we have established a formal training program for grants associates, and we now have a group of some nine potential top scientist administrators in training. We have also run special training seminars for our staff currently occupying grants management positions and intend to invite grantee institutions to send representatives to these seminars in the future.

I will say that these increased activities have been broadly responsible for adding a number of scientist administrators, grants management staff and clerical support. These are located both in the Division of Research Grants and decentralized to our Institutes and program divisions.

You cannot undertake this type of surveillance of our grant activity that we have initiated without broadly expanding personnel.

In general, I would summarize as follows: Dr. Allen's appointment to the grants policy position downtown was one step; the identification of the Division of Research Grants under NIH as a single grants manager for the service is another; and the strengthening of our Institute grants management components is still a third. I would say that these are some of the specific movements of an administrative nature which should give us much closer control over the operations.

Mr. Seggel points out that we have this report that goes into some detail, area by area, of what we have done. I think, sir, that you might have an interest in it.

Mr. FOGARTY. We will put it in the record.

I have one more question in this area so we will place the report in the record following your answer to this question.

Dr. SHANNON. Yes.

REACTION OF UNIVERSITIES TO TIGHTER ADMINISTRATION

Mr. FOGARTY. In summary, Dr. Shannon, I would be interested in knowing what reaction you are finding in the colleges and universities.

Do they regard these efforts with any enthusiasm, or are they concerned about possible Federal restrictions on educational independence?

Dr. SHANNON. Well, Mr. Fogarty, they view them with mixed reactions. In the first place, they all agree something must be done to tighten up their own administrative procedures and something must be done to clarify their relationship with ours in the sharing of this responsibility.

I might say that we have been most impressed by the cooperative spirit with which they are approaching these problems in the meetings that we have had with them.

I think in the aggregate now, we have had a series of some 4 meetings with the executive group of the Association of the American Medical Colleges, and I believe as many as 11 regional meetings were held with medical school deans and some 3 meetings with representatives with comparable positions of responsibility in universities.

On the other hand, while they are giving full cooperation, they have expressed very serious concern that these administrative controls may become too restrictive. They feel it is important that our interpretation of what administrative controls are necessary is in fact acceptable to the Congress. Further, if it is possible to work out mechanisms for decentralization of decision in a very responsible way, then they think on balance, good has come of the program.

But they say if, on the other hand, this is the first step in a series of rigid controls, then on balance this is bad and the savings of dollars in no way can counteract the loss to American science. So that I would summarize, they are cooperative and understanding at the present time, but they view with some apprehension what this means for the future.

ACTION TAKEN TO STRENGTHEN RESEARCH AND TRAINING GRANT PROGRAM

Mr. FOGARTY. I think you have given us an excellent report and that you have shown a very admirable willingness to accept criticism and do something about it when it is well founded.

We will put your prepared report in the record at this point.
(The report referred to follows:)

ACTIONS TAKEN BY THE PUBLIC HEALTH SERVICE TO STRENGTHEN ITS RESEARCH AND TRAINING GRANT PROGRAMS

I. PROGRAM PERSPECTIVES AND PROBLEMS

Before discussing the actions the Public Health Service has taken to strengthen the administration of its grant programs, it is appropriate that these actions be placed in their historical setting together with the program objectives we seek to achieve.

A. THE EFFECT OF PROGRAM AND BUDGETARY GROWTH

In the past 10 years, NIH's support of extramural research has multiplied almost twentyfold (\$40 to \$715 million); in the past 5 years alone, it has more than quadrupled (\$147 to \$715 million).

In this same 10-year span the number of individual research projects supported has increased from approximately 2,000 to 14,000. Also, during these years we have added broad program grants, center grants, special resource grants, general research support grants, and extended our grant support abroad. This growth in both size and complexity has placed NIH in a new position—as a broad supporter of a major segment of science—a role quite different in its relationship both to investigators and institutions than its earlier one as a relatively small contributor to on-going research.

While this growth and the changing nature of our support role have signified an extremely productive period for medical research, it is impossible to grow at such a rate and to take on new programs without experiencing the administrative difficulties which necessarily accompany such basic changes. Our problem is to adjust to these changes while at the same time maintaining those basic values and concepts which have proved so fruitful in producing scientific results.

B. THE PROBLEMS THAT FACE US

1. *Spending and accounting for large dollars*

Basically we are involved in a broad and complex support program but still in a period of transition from a system that was constructed for administering relatively small outlays. We are attempting to provide funds for thousands of research projects and to account for the use of these funds from a single geographical point. Our problem therefore has been to improve the management of grant funds while protecting the essential strength of the research project system. We have been intensively engaged in trying to make this transition a smooth one.

2. *Maintaining the scientific freedom of the investigator*

The efficacy of the NIH research support programs is traceable directly to the primacy of the investigator's freedom to conduct his own research. Money, alone, would not have done the job. Freedom is the other essential ingredient. Freedom is not something valuable or useful in itself. It has been proved to be effective in bringing forth research findings. Freedom is defended not on abstract grounds, or as an inherent right of scientists, but as the prime condition for assuring maximum yield on the taxpayer's investment in medical research.

Yet we know this freedom must be maintained through new means of administering and accounting for our research funds.

3. *Strengthening the capacity of the grantee institution to administer funds*

We believe that one of the keys to solving the problem of maintaining our basic program objectives while at the same time constructing a logical system of fund accountability lies in emphasizing the great responsibility that grantee institutions have for administering grant funds and in assisting them in the effective discharge of this responsibility. Such action must take place within the framework of clear policy guidelines provided to grantee institutions by the Government and assistance to them in the development of effective measures of program and fiscal reviews.

Until recently, few academic institutions have had to deal with research involving a great deal of money. Academic traditions do not in general promote businesslike handling of grant affairs. Most fundamental, however, is the fact that few universities and medical schools have had the resources required to administer with full effectiveness a large and growing set of research programs. The recent increase to 20 percent of the amount allowed for support of indirect costs resulting from grants, and the President's proposal to remove this limitation, if approved, will assist in providing the financial resources. The next section outlines those steps we have taken or intend to take to provide the administrative wherewithal.

II. ACTIONS TAKEN OR PLANNED TO IMPROVE THE ADMINISTRATION OF GRANTS

In line with the perspectives discussed in the preceding section, we have attempted to organize our efforts to improve the administration of our grant programs into several major objectives:

- (a) Take those steps necessary to assure that expenditures from grant funds are made for and essential to the purposes for which the grant was made;
- (b) Provide a greater awareness on the part of grantee institutions of the responsibilities imposed upon them in the acceptance of grant funds and also make certain that they have adequate means to discharge such obligations;
- (c) Assure a more complete and orderly establishment and issuance of regulations, policies, and procedures pertaining to grants administration;
- (d) Strengthen our own internal grants organization, staffing, and processes; and
- (e) Delineate more clearly and improve the executive and advisory functions in the planning and direction of grant programs.

Steps taken or planned under each of these objectives are described below.

A. TAKE THOSE STEPS NECESSARY TO ASSURE THAT EXPENDITURES FROM GRANT FUNDS ARE MADE FOR AND ESSENTIAL TO THE PURPOSES FOR WHICH THE GRANT WAS MADE

In discussing below the policy guides that have been provided to grantee institutions, we describe the development and issuance of a research grants manual. Within that manual we have included a number of key policies which are directed specifically toward assuring that grant funds are expended only for the purposes for which the grant was made. The policies listed below were of such importance that they were reviewed by the Office of the Secretary prior to issuance. Each of them went into effect in January 1963.

1. *Salaries charged to grants.*—Salaries paid from grants must be consistent with salaries which are paid from institution funds to other staff with similar qualifications, and the salaries charged to grants must reflect the actual percentage of the person's time or effort devoted to grants as computed from quarterly "effort" reports made by the investigators and maintained by the grantee institution. In sum this policy provides that there shall be no salary differential which results from the fact that a scientist is paid from PHS rather than grantee institution funds:

2. *Equipment.*—Equipment required for the conduct of a Public Health Service supported grant may be purchased only after determination by an appropriate administrative official of the grantee institution that no equivalent equipment is available for the intended use. Grant funds may not be used for the purchase of any single unit or piece of equipment costing in excess of \$1,000 which has not received prior PHS approval, and grant funds may not be used to equip or furnish offices, reception rooms, conference rooms, or similar space, unless specifically approved by the PHS.

3. *Travel.*—Grant funds may be used for domestic or international travel by individuals engaged in carrying out the approved project where such travel is essential to the successful prosecution of the research being supported, up to the amount specified in the approved application. In exceptional cases funds may be transferred to the travel category if adequately justified in a request approved by the responsible budget official of the grantee institution and by the Public Health Service.

Special provisions which apply to foreign travel which is not specifically approved as part of the grant award include: (a) the investigator must submit a request in writing to the PHS prior to the proposed travel and receive written approval in response; (b) the request must indicate why the proposed travel is needed for effective performance of the project supported by the grant; and (c) the request must be countersigned by the responsible grantee institution official indicating that the travel is in conformity with the institution's own policies on foreign travel.

4. *Charges for alterations and renovations.*—Alterations and renovations may be approved as an appropriate charge to a research grant if they are essential to the conduct of a research project or projects, if they meet the requirements set forth in the specific definition of alterations and renovations listed in the manual, and if the aggregate cost to the PHS does not exceed \$50,000.

5. *Transfer of funds between categories of expenditure.*—For purposes of evaluating applications for research grants, proposed direct costs must be broken down by category of expense; however, after a grant is awarded to the institution, funds may be rebudgeted, except that funds may not be rebudgeted into the following categories without prior PHS approval: alterations and renovations; patient costs; publication of books, monographs or pamphlets; travel, fixed equipment; items of movable equipment costing more than \$1,000; and equipping and furnishing of offices, conference rooms, reception rooms, or similar space.

6. *Changes in project contents.*—The investigator may make changes in methodology, approach, or other aspects of the project which in his judgment would expedite achievement of the research objectives of the project; however, no change may be made, without prior approval of the PHS, which would constitute a significant deviation from the nature and purpose of the approved project.

7. *Discontinuation of grants to profitmaking institutions.*—A key policy which has since been adopted on a departmentwide basis is our decision to use the contract mechanism for research performed by profitmaking organizations, to discontinue all current grants to such organizations and determine which of them should be switched to contracts, and to prohibit further grants to these organizations.

B. PROVIDE A GREATER AWARENESS ON THE PART OF GRANTEE INSTITUTIONS OF THE RESPONSIBILITIES IMPOSED UPON THEM IN THE ACCEPTANCE OF GRANT FUNDS AND ALSO MAKE CERTAIN THAT THEY HAVE ADEQUATE MEANS TO DISCHARGE SUCH OBLIGATIONS

There are three basic approaches to focusing on the role grantee institutions should play in "managing" grant funds if accountability is to be achieved and if freedom of scientific investigation is to be maintained:

1. *Delineation of the nature of the grant relationship*

It is of key importance that we spell out for both grantee institutions and our own staff the basic elements of the grant relationship. We have attempted to do this quite formally in the preface to our recently issued Research Grants Manual.

It is stated therein that under the terms of the grant the institution and individual concerned enter into a very special relationship with the Public Health Service for the utilization of grant funds. A grant represents a mutual joining of interests on the part of the grantor and the grantee institution in the pursuit of a common objective, in contrast to a contract, wherein the Government lays down the specific terms and conditions and requires a specific end product.

In the grant relationship the grantee assumes with the granting agency the obligation to act in the public interest in achieving the common purpose. This is a relationship of trust which imposes upon the grantee the responsibility:

(a) To assure that the grant funds are utilized for the purpose for which they were given.

(b) To exercise the same probity and prudence in their expenditure that is extended to the use of the grantee institution's own funds.

It is to these broad obligations that a recipient of a Public Health Service grant is accountable. These terms, however, impose a broad responsibility on the Public Health Service to assess the adequacy of the administrative practices and mechanisms employed by the grantee to assure, in general, the conditions of prudence and, specifically, conformity with the terms of the grant and established policies and regulations.

An examination by Public Health staff of the administrative processes, controls, and mechanisms utilized in the expenditures of grant funds will be part of the continuing overview of Public Health Service grant programs in the further administration of these programs.

As a final point of understanding, it is emphasized that in the absence of express Public Health Service policy or guidelines, the principal investigator or program director designated in a Public Health Service grant must act in conformance with the policy and administrative practices of his institution.

2. Coordination of our efforts with universities and university associations

In 1962 we held a formal series of meetings with the deans of medical colleges from each region of the country to discuss with them and seek their advice on the problems that currently exist in administering grant programs and to inform them of the steps we are taking to solve these problems. A similar series of meetings was held in January 1963, the primary purpose of which was to elicit from grantee institutions comments and suggestions relating to the grant manual.

In September 1962 we entered into a contract with the Association of American Medical Colleges wherein they are independently (1) studying the present administrative policies and practices of medical schools; (2) comparing these policies and practices as between schools and also with administrative policies and practices as they are being applied in nonacademic institutions, private businesses, and certain areas of Government; (3) organizing workshop discussions of representatives of each medical school and invitees from nonacademic institutions, private businesses, and Government to the end that the administrative and fiscal problems peculiar to medical schools can be identified and ways and means found for their solution; and (4) preparing a report that can serve as a guide to those medical school administrations who may wish to use it as a point of reference for improving their administrative and fiscal policies and practices.

On a continuing basis we are in touch with and seeking counsel from university officials from all our grantee institutions on their problems, their proposed solutions to these problems, and the steps we can take to assist in solving these problems.

3. Provide to grantee institutions policies, management assistance, evaluation, and training

Greater responsibility for fund accountability can only be placed with grantee institutions if they have available to them a clear set of standards and guides which provide the basic ground rules for spending Government funds. To achieve this goal and also to make more orderly our own internal administration, we have formally codified our policy guidelines in the form of the Research Grants Manual. As we have previously stated, of particular importance is the preface to that manual which sets forth the basic responsibilities of the grantee institution for administering its grant funds and also reaffirms the basic principles of scientific freedom within which these guides will be administered.

In transmitting this manual to grantee institutions, we have asked them to submit to us a formal report of the steps they are taking and the systems they intend to follow to carry out the guides laid down in the manual.

Two other steps which have been taken which will provide grantee institutions with codified and uniform standards are (a) the publication in the Federal Register of the first formal set of regulations on research grants, and (b) the development of a grant brochure which will permit grant investigators and grantee institution officials to refer to one source for a description of the content and eligibility requirements for all grant programs.

As noted in the succeeding section, we are also organizing a strengthened grants management component in the PHS which will have as one of its primary functions assistance to grantee institutions in the installation or strengthening of fund control systems and periodic evaluations through site visits of the effectiveness of these systems. We are also studying the feasibility of establishing a series of field installations which can give more effective help on the scene to investigators and guarantee institution officials and handle problems cooperatively with them. Finally, we are planning at a later date to extend our internal training programs for grants administrators to selected administrative officials from grantee institutions.

C. ASSURE A MORE COMPLETE AND ORDERLY ESTABLISHMENT OF REGULATIONS, POLICIES AND PROCEDURES PERTAINING TO GRANTS ADMINISTRATION

Not only is it necessary to make certain that grantee institutions and PHS staff have available a clear set of policy guides and regulations, it is also essential that these guides reflect an orderly and carefully considered process of development and clearance. To this end we have taken the following steps:

1. *Establish a top policy review committee.*—An Interbureau Advisory Committee on Extramural Affairs (IACEP) has been established to review all proposed grant policies and to recommend action to be taken by the Surgeon General. No grant policies affecting more than one institute or division may be issued with-

out the approval of this committee. Its membership includes the grants policy officer in the Office of the Surgeon General as chairman, one representative from each of the granting agencies of the PHS, and the chief, Division of Research Grants, NIH, as executive secretary.

2. *Establish comparable policy review bodies in the PHS bureaus.*—The NIH and the community health and environmental health components of the Bureau of State Services have each established an Executive Committee for Extramural Affairs (ECEA). All grant policies affecting more than one PHS granting agency are reviewed by each ECEA before being submitted to the IACEP for review.

3. *Establish a policy and procedures office.*—There has been established in the Division of Research Grants, NIH, a policy and procedures office which has the responsibility for: (1) preparing all draft grant policies for review prior to issuance; (2) determining what reviews are necessary before submittal to ECEAs; (3) preparing material for ECEA and IACEP review; (4) issuing all grant policies after IACEP clearance; (5) maintaining the grants manual; and (6) providing staff assistance to persons who wish help with the development and drafting of proposed policies.

4. *Codify policies and procedures for development and issuance of grant policy.*—A formal document has been issued setting forth the ground rules for the development and issuance of grant policy and describing the role of the policy and procedure office.

D. STRENGTHEN OUR OWN INTERNAL GRANTS ORGANIZATION, STAFFING, AND PROCESSES

We are mounting a number of major undertakings to accomplish the objective of strengthening the ability of the PHS to administer its greatly enlarged extramural programs. These steps include:

1. *Identify and strengthen the grant policy coordination role of the Office of the Surgeon General.*—On January 2, there was formally established and filled in the Office of the Surgeon General a top-level grants policy officer position to provide a PHS focus for coordination of grants policies. It is expected that staff will be appointed to assist the grants policy officer. The establishment of this central PHS function will permit the Surgeon General's office to provide full-time policy guidance in extramural affairs and to have a focus for resolving questions of an interbureau nature. It also permits the Division of Research Grants, NIH, to continue as the single grants manager for the entire PHS, since its operating function can now be isolated from those policy direction matters which are more properly performed at the Office of the Surgeon General level.

2. *Identify and strengthen those grants management functions to be performed (1) on a centralized basis by the Division of Research Grants for the whole PHS, and (2) on a decentralized basis by the PHS Institutes and program divisions.*—Two major studies are nearing completion which recommend the division of grants management functions between a central PHS component (Division of Research Grants) and the PHS Institutes and program divisions. These studies also describe the organization and staffing measures which need to be taken to strengthen performance of these functions. Completion of these studies will be followed by an organization order to be issued by the Surgeon General directing the bureaus to put the approved recommendations into effect. Our efforts are directed toward concentrating Division of Research Grants' management functions on across-the-board grants management operations, and on assistance to grantee institutions in the development of fund control systems and general oversight of these systems; and placing with Institutes and program divisions the responsibility for administering individual grants and specific programs. These efforts will also lead to the establishment of grants management components in those institutes and divisions which do not have them and to considerable additional top-level staffing in Division of Research Grants and the Institutes and divisions for both professional and administrative management.

Steps to strengthen our staff have in fact already been taken. During approximately the past 6 months we have added 59 scientist administrators, 31 administrative persons and 35 clerical staff to grants administration in our institutes program divisions and Division of Research Grants. The creation, last July, of a new Division of Research Facilities and Resources was also an important step in increasing our management capabilities in a major segment of our grant programs.

3. *Perform certain grants operations on dispersed basis.*—A PHS study team (devoting full time to this effort) has begun work to establish a pilot grant field unit in the Boston area. This team is charged with developing both the logistics and the substance of a dispersed grant operation. They will work with grantee institutions to determine what grant matters can most profitably be coordinated from a PHS installation located near a complex of university centers and what the relationships would be between the universities and the field installations. They will also work with all PHS components to determine the proper organizational location and staffing of such a unit and its relationship to the Washington-Bethesda operation. The study team will, in addition to its study responsibilities, locate in Boston and operate as an actual pilot unit. The target date for establishment of a permanent unit is July 1, 1963. On the basis of our experience with this unit, we will determine whether to establish similar dispersed grants units in selected geographic areas in which PHS provides major research support.

4. *Strengthen our grant audit operations.*—We are taking steps to improve our grant audit operations as an important instrument through which the Government will make a continuing check on the effectiveness with which grantee institutions are carrying out their fund control responsibilities. We have transferred our grant audit section from our grants review and management organization to the Office of the Director, NIH, in order to assure further independence of grant operations on the part of our auditors. We are also devoting concentrated attention to strengthening both the staffing and procedures of our audit operations. These steps are greatly aided by the availability for the first time in codified form both of formal regulations and of a grants manual. It is possible that these audit operations will be part of the dispersed grant units discussed above.

We are also in process of establishing a comprehensive management audit function in the office of the Director, NIH, which will have as one of its functions a regular review of our grants operations and particularly our system of auditing grants.

5. *Strengthen our processes of making the initial review of grant applications.*—Procedures have been developed to revise grant application forms to provide more information about the investigator's resources and requirements; provide a checklist of items to be reviewed with respect to grant budgets and scientific information; more detailed documentation of information gained on site visits; improve information provided advisory councils through summaries of study section actions; and develop special measures to provide a common source for the compilation of information about grantee institutions and investigators.

6. *Provide more highly trained manpower.*—Special steps have been taken to assure that more highly trained manpower is available to administer grants both within the PHS and in the grantee institutions. We have a number of formal training programs either underway or in final planning stages:

(a) A grants associate program has been started to prepare selected scientists (not currently working in the grant field) for positions in the administration of grants. Nine such persons are currently participating in 1 year of diversified professional training and experience in key grant and award programs and attending a series of seminars on public science policy. Upon completion of the program, these grants associates will be available for permanent assignment to a wide choice of program areas as a science administrator. A special grants associates board oversees this program.

(b) The Division of Research Grants in January conducted a series of seminars for training of grants management personnel. The first series was attended only by PHS grants management people, but it is planned to extend the training to grants administrators in grantee institutions. These seminars are designed to train grants personnel already on the job intensively in grants concepts, regulations and policies.

(c) A special training program is being planned to provide on-the-job training and career planning for PHS scientists working in the extramural field. This program will be directed toward broadening the acquaintance of our professional scientists with public science policy, granting programs of other agencies, and career possibilities throughout the extramural programs of the PHS.

(d) A 2-day orientation seminar was held last October for all new advisory council members and will be held annually from now on in July.

(e) Special training and orientation programs have been instituted on a regular basis for all study section executive secretaries.

E. DELINEATE MORE CLEARLY THE EXECUTIVE AND ADVISORY FUNCTIONS IN THE
PLANNING AND DIRECTION OF GRANT PROGRAMS

In the rapid growth of our highly complex extramural programs, a high degree of dependency has been placed upon the advisory councils and other external consulting and technical groups. Although such groups have served, and will continue to serve, a vital and important role, we must exercise care that this involvement does not obscure the important distinctions that must exist between the executive and advisory process in the direction and administration of Federal programs. To assure that these distinctions are recognized and strengthened, we have taken the following steps:

1. *Establish more formal internal focal points for program planning.*—NIH institute directors and program division chiefs, at the NIH Director's request, submitted formal plans for strengthening their program analysis and planning activities, with particular emphasis on strengthening their staff resources for program planning, on developing the kinds of information required for effective evaluation of program activities, and on providing the analyses and assessments essential to sound program and policy determinations. All institutes and divisions have now appointed a top-level staff member with the basic responsibility for program planning and analysis, and these persons are meeting regularly with the Chief, Office of Program Planning, OD-NIH, to evaluate and assess program plans.

2. *Delineate more clearly the role of advisory councils.*—Discussions are being held with each of our advisory councils and a staff document has been prepared directed toward (1) delineating more clearly the role of advisory councils, and (2) suggesting procedures to enable the councils to complete their work more effectively. Our objective is to emphasize the role of councils in assessing current and future program planning and decreasing the time spent by councils in reviewing individual applications or in commenting on administrative policies and procedures. In line with this objective, we are increasing our own staff preparation of materials for council review and providing the councils with material presenting for their consideration specific problems relating to selected grants. We are also developing policies and procedures to enable PHS staff to negotiate precise budget amounts for grants recommended by the councils.

This description of the background and status of our efforts to improve our administration of our research grant and training programs can perhaps be summarized through the following key points:

First.—We are involved in a new set of relationships in our grant programs. We are no longer merely one among many who support individual research investigations. Our programs have grown so significant on the national scene—both in dollars and in types of support—that we now provide the major source from which medical research derives.

Second.—This fact imposes additional responsibilities both upon us and the recipients of our funds to assure that these resources are used with prudence and with a specific concern that they are spent for the purposes for which the funds were granted.

Third.—We need to continue to explore the measures followed to administer these funds by both the Government and grantee institutions to make certain that they are adapted to this changing situation, and that we can account for the use of these funds to the public which has provided them.

Fourth.—Perhaps, most important, we must make these administrative adaptations in a manner which preserves the essential need of the investigator to pursue his research in a climate of free investigation and at the same time giving clear assurance of proper stewardship in the advancement of sound programs in support of the nation's vital research effort.

Mr. FOGARTY. Mr. Denton.

TITLE TO GRANT PURCHASED EQUIPMENT

Mr. DENTON. You spoke about the fact that a line was drawn at a thousand dollars regarding equipment.

Dr. SHANNON. Yes, sir.

Mr. DENTON. And if the grantee purchased equipment over a thousand dollars, he had to get your permission?

Dr. SHANNON. In either of two ways. He could indicate his need for that piece of equipment in the research grant application and if it is approved there, he gets the money, and can purchase it. But if it is a new need which was not contained within the grant, he must get separate, written permission from us.

Mr. DENTON. Who takes title of that property he purchases?

Dr. SHANNON. The institution, sir.

Mr. DENTON. The college?

Dr. SHANNON. Yes, sir.

Mr. DENTON. Now, is that taken out of the grant money?

Dr. SHANNON. Yes, sir.

Mr. DENTON. One thing that the Fountain report criticized was the way you kept inventory.

Dr. SHANNON. Yes, sir.

Mr. DENTON. They said many times people were permitted to purchase equipment when it was available in the NIH's hands or in another institution that had purchased it with NIH funds.

Am I right about that?

Dr. SHANNON. In substance you are completely right. But the point was not so much that an inventory should be kept of NIH-owned property but rather an inventory was not kept of property that was purchased with NIH funds.

We pointed out to the committee that we felt such an inventory would not be a useful one because knowledge of the availability of a given number of centrifuges in a given environment without comparable knowledge of the total program of that environment would not permit a judgment as to whether a centrifuge was in excess and not needed.

On the other hand, we do agree with the Fountain committee that there must be a much more formal review of the need for a piece of equipment. A simple indication on the part of an investigator that he wants to buy a piece of equipment is not enough.

But we feel that with suitable administrative devices within the university, through the business office or by a scientific advisory committee the scientific need for these things could be determined locally with all the circumstances known.

Mr. DENTON. If the institution buys equipment and keeps title to it is not that taken into account by the grant committee?

Dr. SHANNON. When grants are made it is very difficult to be very specific about each piece of equipment since it is difficult to determine how the study will evolve over a period of time.

Mr. KELLY. I do not know quite what you mean by taking into account.

It has been the policy of NIH to recognize that the——

Mr. DENTON. If the grant is \$10,000 and they have got to buy a certain piece of equipment, is that deducted from the \$10,000 or taken into account?

Mr. KELLY. A total amount, if it is needed in the equipment category is made available to them. The theory has been that one of the purposes of the Public Health Service grant mechanism has been to improve the research capability of the institution and by allowing them to keep the equipment, it does improve their capabilities, so that the grant does cover that item.

The Congress recognized that this was a valid concept, and enacted a law which said that any granting agency could leave title to equipment to a college and university.

Mr. DENTON. It does seem to me if they need that piece of equipment for their project and the Government pays for it, that then it ought to belong to the Government and not to the institution when they get through.

Mr. KELLY. This was the approach which was used with respect to research contracts, and when the NIH took over some research contracts they had to maintain an accountability of this as Federal property. The nature of grant support was considered to be incompatible with this approach, and the Congress actually authorized all of the agencies to do what NIH is doing for colleges and universities.

POLICY ON PATENTS

Mr. DENTON. Let me ask a related question. What about the patents when there is a case of patentability?

What policy do you pursue on that?

Dr. SHANNON. Mr. Denton, what I would suggest is you let us present to you a staff document that outlines some of the problems in the patent area that are not fully resolved at the present time rather than try to discuss it now.

Mr. DENTON. I do not pretend to be a patent lawyer, but I do know that if anybody but Government hired a man to do research work and a patent was developed, the man paying for it would get the patent.

But all through the Government we run into a situation where the Government hires a man and when the man makes an invention he gets the patent and the Government only has a license.

Dr. SHANNON. We certainly do not subscribe to that attitude as a reasonable one. It is so complex that I just could not attempt to explain the complexities briefly.

Mr. FOGARTY. Dr. Endicott can explain that.

Dr. TERRY. Yes, sir, he can. As a part of this problem, however, it has been necessary for me to establish in the Office of the Surgeon General a patent review office. This is under the direction staffwise of Dr. David Price, my deputy. When he is up testifying on that, he would, I think, be in a better position than anyone else to explain our patent policies because he is a member of the Departmental Patent Board representing the Public Health Service, and he is in charge of the administration of the patent policy within the Public Health Service.

So, if we may, I would like very much for any questions that you have on patents to be discussed at that time.

COMMITTEE ROLE IN EXPANDING MEDICAL RESEARCH

Mr. FOGARTY. Dr. Shannon, you have been appearing before this committee now in connection with appropriations for the Institutes of Health as its Director for 7 years.

During that time I think you would agree that this committee and Congress have been responsive to the need to strengthen and expand this Nation's capacity for productive medical research.

Dr. SHANNON. Yes, sir, Mr. Fogarty, I think if it were not for actions taken by this committee and its counterpart in the Senate, we would not have productive capacity to do the work we are doing now nor would we have achieved a rate of leadership in the areas of general responsibility for medical research.

Mr. FOGARTY. At the time you first appeared as Director of NIH, there was a significant change in the gentle upward curve of Federal expenditures for medical research.

Dr. SHANNON. Well, that I covered in the review of the charts earlier in the testimony, Mr. Fogarty.

I became Director of the NIH the summer of 1956 and my first contact with problems of running the program was a series of conferences that I had with Secretary Folsom that summer.

Were you there, Mr. Kelly? It was really, I think, a historic summer from the standpoint of Federal attitudes toward medical research, because as I pointed out earlier, certain broad general decisions were made at that time that would modify the program development. I might say, one of the things that has made this possible is that for the first time the executive branch agreed wholeheartedly with the two Appropriations Committees that the expansion of this area was of vital concern to the health of the Nation and agreed to go forward.

PROGRESS MADE WITH INCREASED FUNDS

Mr. FOGARTY. Would you say then that appropriations recommended by this committee and passed by the Congress have played a significant role in keeping this Nation the leader in health and medical research?

Dr. SHANNON. I would, sir, and I would emphasize again, that had the progress during the past 5 years been patterned after that of the early 1950's, it would take some 10 years to get where we are today.

Now, I would like to comment a little on the side about what I mean where we are today.

By this I mean the number of well-trained, productive scientists, housed in adequate physical facilities and addressing themselves to important problems involved in medicine and having either direct or indirect bearing on serious diseases.

The growth has been nothing short of phenomenal and I think that while I said earlier that science, the quality of science and biology and medicine can be no better within the NIH programs than the quality of science across the Nation, I think it is pertinent to point out that the quality of science across the Nation has been tremendously improved by these programs.

Dr. TERRY. Are you going to elaborate what you meant by 10 years?

Dr. SHANNON. I think this way: If you take the increases in budget beginning in 1957 which I think was about 30 percent for the year, and Mr. Fogarty, this is not to suggest that we should project for all time a 30 percent per year increase, but it is to say that this 30 percent in that year occurred at a very critical time in the development of medical science and at a time when the physical sciences were growing.

Had we retained the rate of increase that characterized the operation before that summer of 1956 we would not have achieved our present capacity, until about 1967. So that one can very realistically

say a good part of the productivity of our present bioscience plant that we have today, and indeed what need be accomplished in the next 10-year period is as a result of the rapid acceleration in the past 5 years—in other words we have really bought time.

Now this is not to say that time multiplied by dollars equals results. But in a broad sense this is true.

NIH RESEARCH CONTRIBUTIONS

MR. FOGARTY. How does that compare with the statements of some Members of Congress who say the Institutes of Health are not responsible for the gains that have been made in the last 10 years; that the Institutes of Health cannot take credit for the advances in medicine that have occurred during the last 10 years?

DR. SHANNON. I would say there are very few major gains in the past 5 years that cannot be traced either directly or indirectly to the programs at the National Institutes of Health.

Directly, insofar as our contribution has been to direct support of the scientists who contributed to the advance, or indirectly in that the funds from non-Federal sources, are now supporting individuals that in the absence of the broad training and research opportunities made possible by Federal funds would not have entered the field of biology and medicine.

I think that when you are at the level of support that our programs are it is very difficult to find any broad significant advance in medicine that cannot be rationalized as being at least in part, and no small part, due to the Federal entry into support of science on a very broad front.

MR. FOGARTY. Other than more research underway, more people now in the Nation's manpower pool, and more facilities throughout the country, what does this mean?

DR. SHANNON. Well I think probably most importantly it means that the whole character of the medical sciences has changed.

I think our activities today are greater in breadth, greater degree of penetration than was possible before this took place.

I think our ability to maintain and keep pace with the development of mathematics, physical sciences, engineering has permitted those elements or elements of the physical sciences to broadly participate in the development of medical advances.

Because of this support we are in a good position to take advantage of computer technology, model simulation, and electronic developments that have been so helpful in advancing scientific work in other fields.

I think it is possible for us to use broad multidisciplinary types of approaches, using highly sophisticated technology which heretofore has not been possible.

I think it is possible to enter such broad fields as epidemiological research and study of the diverse characteristics of large population groups both in this country and abroad—very costly, very expensive work—not as an end in itself but to seek clarification of disease phenomena where, without this type of research, clarification or understanding is impossible.

I think for the first time in this country, broadly spread throughout the country, as opposed to simply in Bethesda, we have modern

clinical research facilities for the serious exploration of disease directly in man.

I might point out that these clinical research facilities are expensive resources although essential resources. There is little point in establishing a very broad laboratory activity unless one provides for the definitive application of such knowledge in the human subject in a controlled clinical setting.

So that I do not look upon the advances of medicine, the advances of medical research as the simple end result of a game in numerology.

I think more important than the numbers are the major qualitative changes for the better that have occurred in almost every element of the medical sciences.

Mr. FOGARTY. Now I would like to get down to specifics. I would like to ask you about some of the statements that have been made and the articles that have been written that give the public a general impression that the Congress has been pressing money on you and your colleagues at NIH at far too great a rate.

GRANT ADVISORY AND REVIEW GROUPS

What about the statement that NIH relies on a veritable "Who's Who" of medical research as its advisers and at the same time makes these same individuals the main recipients of its funds?

Dr. SHANNON. In a certain respect this statement is correct. But the facts have been greatly misrepresented.

In part, it stems from the basic convention that an essential element of the grant process is the obtaining of competent advice from scientists who are expert in the particular fields through the medium of advisory committees and review panels.

These men are chosen because of their activity in the field, their reputation, and productivity. We have some 200 of these advisory and review groups. Some are quite small and some are quite large.

Dr. TERRY. If I may mention there, I just had occasion to check and as of the time we issued our roster of consultants and advisers to the Public Health Service, December 1962, there were 1,797 consultants.

Dr. SHANNON. Now these people, being the best people we can select for advice, obviously are going to make out very well in competition for grant funds.

We have been criticized. We say that we require an individual who is concerned with a grant or whose institution is concerned with a grant to absent himself from discussions of such proposals.

But it is argued that this does not make any difference. This general unsupported charge has been made so often that our advisory groups are very sensitive about it and they bend over backward to avoid any semblance of special consideration.

We have analyzed our grant program from the standpoint of the approval rate of grants to institutions before they had advisers and after they had advisers on study sections, for small institutions with very few advisers as opposed to large institutions from which we may draw a larger number of advisers, in terms of study section actions and in terms of council actions, and we cannot come up with anything but evidence opposed to the concept that review processes are anything but objective.

I might say that the system we use is the same system used by the National Science Foundation, by other Federal agencies.

Mr. FOGARTY. They copied it from you, did they not?

Dr. SHANNON. This process had its origins with the private foundations. But I have a very telling comment if I could read it into the record. I would like to.

Mr. FOGARTY. Go ahead.

AMA COMMENTS ON REVIEW PROCEDURE

Dr. SHANNON. This is a quote from a recent report from the Council on Medical Education and Research of the American Medical Association.

I think they are in a position to be fairly objective because they were looking at our support programs in trying to find out whether they were helpful or harmful to the educational process.

They concluded in general they were broadly helpful but in their report they said this, and I quote:

Grants from NIH are awarded only after careful review of each application by study sections composed of leading scientists, many of them members of a medical school faculty. Following this, the applications are approved by an advisory council consisting of outstanding citizens. This system has been applauded by educators, scientists, Congressmen, and others. The system has been copied, with modifications, by other agencies, including many of the voluntary health agencies.

I, sir, cannot be any more strongly in support of the device than the Council on Medical Education and Research of the AMA is in a statement such as that.

LAY REPRESENTATION ON ADVISORY GROUPS

Mr. FOGARTY. Now, I have heard a view expressed that laymen are not adequately represented on the advisory groups upon which the Public Health Service and the NIH depend in the conduct of these programs.

What is your view on this matter?

Dr. SHANNON. Mr. Fogarty, I realize that this is a not uncommon criticism of our advisory structure. And as I have said before this committee, the dominance of the advisory structure by scientists could well cause concern on the part of nonscientists in the public, particularly those who do not have a deep understanding of our mechanisms.

First, I say I believe that as with the military, scientists should be controlled by nonscientists in terms of the resources that are available to them in the same way the military is controlled by civilians.

On the other hand, the types of decisions that our advisory groups make fall into two distinct categories.

The first is a straight technical decision that assesses the competence of the scientist, the resources that are available to him, the administrative support he obtains from his institution, and the reasonableness of his prospective investment. This is a judgment in which the layman cannot participate in an intelligent way and this must be made by the scientists and by the best scientists that are available.

SUPPORT FOR MORE SCIENTISTS

Mr. FOGARTY. It has been said that increased appropriations to NIH for research make it easy for more and more scientists to find support. Is this true?

Dr. SHANNON. Mr. Fogarty, it depends entirely upon how that statement is made as to whether it is true or not. With the expansion of appropriations, it is certainly possible to support more scientists. On the other hand, I would not say it is easier for the individual scientist who has a project to find support. I point out that the approval rate of research grants has dropped in the period 1957-61 and this during a period of time when the budget has increased from \$183 to \$560 million. In 1957 the approval rate in terms of number of grants made out of the number reviewed was 75 percent. Now it is 56 percent. But more importantly, in terms of the dollars requested, the approval rate has dropped from 70 to 44 percent. We feel that while this does not prove more rigid or more effective criteria of assessment, nonetheless it is indicative that there has not been a broad relaxation of guidelines. I might say that even in periods wherein we have turned back balances because we have felt the expenditure was unwise, we tended to tighten up on our approvals. We have had in being for 2 years now a procedure that has precluded, without special affirmation action by an advisory council, those research grant applications that fall in the lower 10 percent of the priority ratings assigned by each study section. Now, our councils have found this a rather arbitrary way of assuring increased excellence and we have attempted to relax the rigidity of this special review, but at the same time, to provide very careful, individual staff review of those proposals that fall in the lower priority ranges. Actually, this additional review procedure was put in primarily because we wanted to be certain that simple pressure of dollar funds did not result in a simple relaxation of the mechanisms. I don't think there can be any proof adduced to show that our review mechanism is better or worse now than it was 10 years ago. And, sir, I would say that I am not impressed by reputable people who make the broad statement that we are relaxing our reviewing mechanisms. I would point out, too, that comparisons have been made between review procedures in the National Science Foundation and review procedures in the National Institutes of Health. It has been pointed out that percentage-wise approvals are less in NSF than those in NIH. But, Mr. Fogarty, please believe me, this does not indicate that NIH is lax in its review mechanisms. This is a reflection of the condition pointed out in the President's budget that the fund made available to the National Science Foundation has been grossly inadequate to support research grants in areas of great importance to the Nation and year after year they have been unable to support many worthwhile projects. Measures basically reflective of ability to pay as is determined by budget inadequacies has very little to do with the qualitative character of the review process.

The President is asking for a significant increase in the National Science Foundation. Thus the review percentage at NSF depends more on Appropriation Committee action and determination of the amount of funds available than the actual mechanics of the review

process. One can quarrel with the amounts of funds that are made available to the two organizations, but one cannot just use the figures to establish the relative excellence of the two reviewing mechanisms.

USE OF FUNDS IN EXCESS OF PRESIDENT'S BUDGET

Mr. FOGARTY. As you know, congressional appropriations have generally exceeded the administration budget. It has been said that this congressional action has led to "waste on a grand scale," and the National Institutes of Health has felt itself under pressure to spend all of the funds appropriated to prevent their reverting to the Treasury. Would you comment on these allegations?

Dr. SHANNON. I can only comment in one fashion and that is to say that the allegations to my mind are quite untrue. I believe the record shows that NIH has consistently turned back funds and appropriations where they are in excess. I think every action we have taken has shown a mature approach to the problem of developing a program where in dollars available it is not the primary limitation. I think that a loose statement of this sort without any support of a factual nature is nothing but detrimental to science in general. Unfortunately, these statements are made by individuals in very responsible positions who should know better but quite obviously do not.

I would say that the individual Members of Congress who have to sit on an appropriations committee like this might well take the listing of grants in their own State and if funds are spent grossly in excess of the needs or in an indiscriminate fashion across the Nation, then this would be true in any of the large States with very large programs. I think if the individual members of the committee will discuss this program within the academic environment that they have a very good acquaintance with, they can find within that environment evidence to enable them to judge the accuracy of such allegations.

EFFECT OF INCREASED FUNDS ON QUALITY OF RESEARCH

Mr. FOGARTY. What about the comment that the large amount of funds appropriated by the Congress may constitute a threat to the quality of scientific work being done by forcing scientists to spend rather than to think, and turning them into administrators?

Dr. SHANNON. Well, Mr. Chairman, there is no direct answer to that. There is no doubt that as the science plan of the Nation expands, that it requires more intelligent administrators and hopefully some of these would come from the ranks of science. There is also no doubt that as one develops much more complex experimental situations involving many disciplines, many scientists and at times many institutions, that the administrative apparatus must be manned at least in part by competent scientists. But, this is the price of progress. This is the price one must pay for the undertaking of performance of work of this sort. I think that the charge that this is bad cannot be sustained; that science administration becomes an important problem to the scientist himself is true, but the question is, is this too large a price to pay for a broadly aggressive program involving as it does the training of large numbers of very competent scientists and providing them with the wherewithal for productive work. I do not believe the price is too great.

CANCER CHEMOTHERAPY PROGRAM

About the cancer chemotherapy program, it has been reported that this program is an outstanding example of outside political pressure. Presumably pressure on the NIH. I do not look upon it as pressure. I think the development of cancer chemotherapy is an example of the development of the program where there is no unanimity of agreement on a professional level, either during the initial stages of the program or during the period of rapid development. I might say that Dr. Endicott, who is here, and the director of the program at the time, will remember the very positive way I insisted that for a 2-year period it not expand, that it shake the bugs out of its apparatus and firm up its procedures, and more clearly identify its objectives. You will recall, Mr. Fogarty, that we testified to that effect before this committee. The committee did not insist regardless of those judgments that the program expand and after the 2-year assessment we came back and defined for you where we thought the program could go. If this is pressure it is on professional rather than political grounds.

Mr. FOGARTY. So that in fact there was no so-called striking example of outside political pressure to do this?

Dr. SHANNON. I would agree, sir.

Mr. FOGARTY. It is also said that because of the cancer chemotherapy program, other programs are being shortchanged and that certain popular areas of cancer research, namely, chemotherapy, radiation and viral etiology are being supported to the exclusion of other possible approaches. Is that so?

Dr. SHANNON. I don't believe it is, sir. As we pointed out to this committee on several occasions, a good deal of the expansion of the cancer chemotherapy program has been the result of the utilization of scientific personnel or professional personnel that would not otherwise be engaged in our programs.

This drawing into the research program of new scientific talent, accompanied by a very rigorous type of program for the production of new scientists has permitted the cancer chemotherapy program to progress and progress soundly without in any way detracting from the other fields. So I would say that the allegation has no basis in fact.

Mr. FOGARTY. All right, is there anything else you want to say on this general subject?

Dr. SHANNON. No, sir.

MEETING NEEDS FOR MEDICAL RESEARCH MANPOWER

Mr. FOGARTY. Including this budget request, what has been done since your report on manpower for medical research was issued, to meet the needs that report showed to exist?

Dr. SHANNON. Mr. Fogarty, this has been analyzed at our request and we will pick out the specific parts that cover manpower training and combine them. In general, you may recall that we set out certain specifics. One of these was to expand predoctorate training so we would participate most effectively in the production of scientists rather than to bring scientists into our fields from other fields.

Another was to develop a system of science education within the medical schools aimed directly at the production of scientists. Our progress along this line will be submitted for the record.

(The information follows:)

STRATEGIC OBJECTIVES FOR TRAINING ACTIVITIES—NIH FISCAL YEAR 1964 BUDGET

The general objectives of NIH training activities over the period extending to 1970 were presented in testimony before the House Committee on Appropriations in the hearings on the fiscal year 1963 budget of NIH. They are as follows:

1. The central goal of NIH programs is to insure that trained scientists and physicians are available to staff a national medical research effort that will involve a total national investment approximating \$3 billion by 1970. In gross quantitative terms, the Nation's total supply of medical research manpower will have to double between 1963 and 1970. The funds provided by NIH will supplement those available from other governmental and private sources. As is the case with research support, it is evident that private sources alone will not be adequate to finance the needed expansion.

2. Attainment of this goal will require continuing quantitative expansion, and shifting patterns of training, so far as NIH programs are concerned. A major development over the years immediately ahead will be increasing dependence upon increasing the total pool of trained people from whom the group of scientists will be drawn. This will require extensive construction and provision of increased operating funds to graduate and professional schools.

3. The proper rate of growth of NIH training funds cannot be foreseen with precision because NIH is not responsible for financing the Nation's total training effort. The availability of funds from other governmental and private sources, and the purposes for which these funds are available, will influence the magnitude of the NIH effort.

In translating these general objectives into terms of the elements of the proposed fiscal year 1964 budget relating to the training of manpower, the following facts are relevant:

1. All kinds of fellowship and training grants financed by NIH will increase from the 1963 apportionment level of \$190 to \$218 million in the proposed 1964 budget. This is an increase of \$28 million, or 15 percent.

2. The number of people in training will increase not by 15 percent but by about 10 percent. The number of people trained increases at a less rapid rate than the total training investment because an increasing proportion of the training funds must go to that portion of the costs of training represented by strengthening the training institutions as contrasted with support of individuals.

3. A 10 percent per year compound annual increase in the number of persons trained would approximately double the number of persons in training between 1963 and 1970. However, it must be realized that much of the increase proposed in training budgets is (as pointed out below) for the training of service personnel in the field of mental health, rather than for the training of research personnel.

4. In terms of orders of magnitude of training budgets, the proposed increase for fiscal year 1964 is generally consistent with the long-range training goal, with the reservation that it may be somewhat low. The range of uncertainty relates first to the unpredictability of the costs of training, a factor which will certainly continue to rise but at a rate which cannot be precisely foreseen. The second area of uncertainty is the proportion of training funds that will be used to train service personnel. The third area of uncertainty relates to the availability of funds from other governmental and private sources. The proposed budget rests upon a generally optimistic view of the availability of funds from private and other governmental sources.

5. In terms of the division of effort between fellowships and training grants, there is little change as between 1963 and 1964. In both years, about 80 percent of the funds are for training grants and 20 percent for fellowships.

6. Within the categories of fellowships, predoctoral fellowship funds are proposed to increase by 26 percent, whereas postdoctoral fellowship funds are proposed to increase by half as much—13 percent. This is in line with a general decision to stress recruitment to the academic disciplines related to health and medicine.

7. The research career award program is proposed for expansion from \$18.7 to \$19.4 million, or about 4 percent. It is entirely possible that the expressed needs for career support will expand rapidly in the year ahead.

8. Support for undergraduate training through undergraduate training grants will remain virtually constant as \$14.5 million in fiscal year 1964. The role of the Federal Government in this area is under review by the Congress, and existing programs will not be extended until more general decisions have been made.

9. Of the \$28 million increase proposed in NIH budget items relating to training, \$20 million is concentrated in graduate training grants. Extensive recent discussions in 25 universities have reconfirmed the fact that these grants, which provide support both for the cost of training and for the support of advanced students, are among the most valuable—and valued—form of aid to the development of scientific manpower available through NIH.

10. Of the total increase in training funds, about 70 percent is concentrated in the \$20 million increase from \$55 to \$75 million in the training activities of the National Institute of Mental Health. Most of this increase, in contrast with the activities of the other Institutes, will support the training of people for service rather than research activities.

Dr. SHANNON. A third, particularly relevant to the development of the child institute was to emphasize training in the behavioral sciences.

These were the main program thrusts of our program during the past year and each Institute has conducted its affairs in an attempt to achieve within its own category some progress along these lines. In my professional opinion, what we will be able to do in the immediate future—the next fiscal year—to train scientific manpower will be at a minimum level required for the attainment of our long-range goals. I will submit for the record an analysis of the reasons why we think this is the case.

I might say as an aside that this year we, in accord with the NSF, have agreed that for each of the predoctorate fellowships, it would be equitable to pay the university, itself, \$2,500 to cover the cost of educating the predoctoral student. This increased the total cost of each fellowship and reduced the number of awards we could make.

Mr. FOGARTY. In your professional opinion what more should we be doing now and in the immediate future?

Dr. SHANNON. I would say that the goals and objectives we outlined in the manpower report last year basically obtain to the present time. I think that I wouldn't modify that report today.

RESEARCH USING ANIMALS

Mr. FOGARTY. Newspapers and periodicals continue to poke fun at the medical research using animals, like this recent one, "Monkeying With Arithmetic—Lights Flash and Chimps Shriek for Science's Sake." You got up a pretty good statement on this last year. Would you bring it up to date and place it in this year's hearing record?

Dr. SHANNON. Yes, sir.

(The information follows:)

SUMMARY STATEMENT CONCERNING NATIONAL INSTITUTE OF MENTAL HEALTH, SUPPORT OF DR. HARRY HARLOW, UNIVERSITY OF WISCONSIN, M-4528 (FORMERLY M-772)

Dr. Harlow received a Public Health Service research grant award for the first time in 1954, but he had been active for 20 years before that in extensive research on behavior in the rhesus monkey—studies evaluating the perceptual

and intellectual skills of these animals. At the time he submitted his first application to the Public Health Service, he had already established one of the better primate laboratories in the country, but his plans to study the social behavior of primates was handicapped by inadequate space and limited staff. The research grant support which he has received has permitted him to expand his work into this general area. Since receiving his first award, Dr. Harlow has initiated a number of behavioral investigations, among which the problem of the effects of mother-infant relationships on the future social development of the animal has occupied a central position. He has developed novel procedures in these investigations, including the use of "artificial mothers" which have shown that the experimental manipulation of the physical characteristics of the "mother" can influence not only the social responses of the infant monkey other infants, but its perceptual and learning capacity as well. Further, these influences are maintained, to a greater or lesser degree, over a long period of time and have a critical effect on the maternal behavior of the adult female, when she has infants of her own. These studies have attracted a great deal of attention and interest from psychiatrists, psychologists, sociologists, psychoanalysts, and anthropologists.

Beyond these studies on infant development, Dr. Harlow and his colleagues have undertaken a variety of investigations: on the developmental aspects of learning and problem solving in monkeys, on motivation, on the development of visual exploration and curiosity, on the effects of cortical lesions in the infant on the subsequent development of behavior, on the effects of induced phenylketonuria (a disorder which, in humans, produces mental deficiency) and others.

His plans for the future call for the continuation and expansion of these projects. He will undertake a series of additional studies on the nature and development of the infant monkey's affection for the mother, the nature and development of affectional patterns among infant monkeys, the affectional patterns of the real mother for the infant, the maturation of learning ability in monkeys up to 4 years of age, the effect of various cortical and subcortical lesions on learned and unlearned behavior, and the nature of the behavioral changes resulting from metabolic disorders in monkeys, including additional work on induced phenylketonuria.

As recently as November 1962, Dr. Harlow and his colleagues reported results of new studies on peer relationships. They have now raised monkeys without mothers but in the company of age-mates; and with mothers but without age-mates.

Two groups of monkeys were taken from their mothers and housed alone in cages with "surrogate" mothers (forms of monkeys made from wire and cloth). They were brought together in a playroom for a daily 20-minute period and, in spite of the relatively limited opportunity for contact, they developed effective play relations. Another group, raised together in a large cage without their mothers or surrogates, also showed similar evidence of an affectional bond. None showed any sign of damage by mother deprivation, and all were normal in their sexual behavior.

In another study, the investigators found that normal mothering alone is not enough to produce socially adequate offspring. Monkeys, raised alone with their mothers for 7 months, were unable to achieve a normal relation when put together. Finally, in a study in which infant monkeys were totally isolated for the first 6 months of life, the investigators concluded that such a period renders an animal permanently inadequate to develop normal behavior in later life. They believe the effects of shorter periods of isolation—60 to 90 days—are clearly reversible.

This research program has been a long-range effort and, in common with many large-scale research undertakings using primates, is expensive. The animal colony must be cared for and plant and equipment costs are fairly high. Through the end of 1961, Dr. Harlow's grant support from the National Institute of Mental Health has totaled \$556,315. He has recently been awarded \$171,925 for the year beginning January 1, 1962, and he has been recommended for an additional 5 years of support contingent on the availability of funds, and on the annual re-

confirmation of the award by the National Advisory Mental Health Council. The annual amounts of the award for the next 5 years are as follows:

1963-----	\$185, 000
1964-----	200, 000
1965-----	215, 000
1966-----	215, 000
1967-----	215, 000

In addition to the support which he has received through the National Institute of Mental Health, Dr. Harlow has also received awards from the National Heart Institute, primarily to cover costs for an addition to the primate laboratory, from the Division of General Medical Sciences for a study of radiation effects, from the Ford Foundation and from the Department of Defense.

All requests for Public Health Service research grant support are reviewed by two groups of non-Federal scientists who serve the Institutes in an advisory capacity. Dr. Harlow's applications have been reviewed and evaluated by the scientists on the study committee for his field of research and then submitted to the National Advisory Mental Health Council, with their recommendation that the application be approved. The Council is established by law and the Surgeon General may not award any grant that this body does not recommend for approval. The Council is composed of 12 members from outside the Government who are distinguished in the fields of medicine, science, education, and public affairs.

In accord with this procedure, Dr. Harlow's research grant applications have been reviewed three times since the original award in 1954; these reviews occurred in June 1957, March 1958, and, most recently, in November 1960. The reviewers in all cases have been uniformly enthusiastic about Dr. Harlow's research. In 1958, for example, the reviewing study section indicated that Dr. Harlow's request for support should be recommended for approval because his developmental study is among the best that has been attempted and it ought to be continued over a longer period of time with an increased number of animals. The reviewers also expressed the opinion that Dr. Harlow's laboratory is the only first-class primate laboratory in the country devoted largely to the study of behavior. Further, both the study section and the National Advisory Mental Health Council felt that Dr. Harlow and his ingenious group could be counted on to uncover many new leads and make new discoveries not now predictable, and that contributions from this laboratory can be expected not only on the maturation of primate behavior, but also on affective behavior, learning, perception, and motivation. Other comments referred to the outstanding effectiveness with which Dr. Harlow has organized this large scale research program, freeing himself from routine duties, so that he can devote his creative talents to the laboratory and to the planning and interpreting of research. One of the additional gains which has resulted from Dr. Harlow's work is the training opportunity which his laboratory affords, on both a predoctoral and postdoctoral level. Scientists who have received this training have been in demand in other laboratories and have made noteworthy contributions in their own right.

It may be appropriate at this point to indicate why sizable amounts of money are spent for animal studies and to clarify the relation of these studies to the problem of mental health. There are several reasons for supporting research of this type. Subhuman primates are the animals most similar to man in physiology and in mental capacity; and, they react to physical stresses, to disease and to psychic disturbances in ways similar to humans. For this reason the monkey kidney was used for the growth of polio virus to produce vaccines; and, a chimpanzee was chosen to ride in our first suborbital tests of a space capsule. Furthermore, it is necessary to undertake comparative studies of the behavior of subhuman species to establish what part of man's behavior is unique and what part is common to primates, to mammals, or to animals in general. This approach is needed to understand the origins of man's behavior and, hence, what facets of his behavior are more readily subject to change with change in environmental influences.

Thus, the National Institute of Mental Health does not support Dr. Harlow's work because we are especially interested in the study of monkey behavior itself, but because we are very interested in the implications which these studies may have for a deeper understanding of human behavior. For example, there is general agreement among mental health practitioners that the nature of the mother-child relationship is critical in the development of a child's ability to

establish healthy and satisfying interpersonal relationships, and there is some reason to believe that it has significant effects on the development of perceptual and intellectual function, also. Systematic evidence on these questions, based on rigorously controlled studies which explore all aspects of the problem, is difficult to obtain, however. For ethical reasons, such investigations often cannot be undertaken with human subjects. Certainly, we cannot experimentally manipulate human mothers and their children to see what kinds of behavioral disturbances the experimental changes will produce in the child as it grows up, but we can do this with animals. The information obtained in research of this type is extremely important in suggesting new theoretical approaches to problems of mental health and in testing old ones. This research is an essential supplement to research performed directly with human subjects and paves the way for new and better human research. The fact that Dr. Harlow's research is described as "a study of affectional ties" is a matter of wording. This represents his shorthand description of a study of the multiple aspects of the mother-child relationship.

With regard to Dr. Harlow himself, it may be worth noting that he has vigorously pursued a distinguished academic and research career ever since he received his doctorate in 1930. He is a full professor of psychology at the University of Wisconsin and has served as chairman of his department. In 1955 he was named George Cary Comstock research professor in psychology at Wisconsin; he was a Carnegie Fellow in Anthropology at Columbia University in 1939-40; he served as Chief of Human Resources Research for the Army in 1950-52, and is a member of the Army Scientific Advisory Panel of the Office of the Secretary of Defense.

Among other honors and distinctions, he has served as editor of the *Journal of Comparative and Physiological Psychology* since 1951, was president of the Midwestern Psychological Association in 1947-48, president of the Division of Anthropology and Psychology of the National Research Council in 1954-56, and president of the American Psychological Association in 1957-58. Ever since 1932 his contributions to the scientific literature have been frequent and of high quality. Since 1954, when he received his first Public Health Service research grant, he has published some two dozen articles in various scientific journals. In 1960 he received the Distinguished Scientific Contribution Citation of the American Psychological Association, which carries with it a \$1,000 award. The citation itself is an indication of the attitude of his scientific colleagues toward Dr. Harlow's work and reads as follows: "For his indefatigable curiosity which has opened up new areas of research in animal behavior and has helped greatly to keep comparative psychology near the center of the psychological stage. Throughout the years his vivid imagination has led to the analysis of many stimulus relationships, the exploratory and manipulatory motives, and the all-but-ubiquitous learning sets. Recently the age-old problem of love has been revitalized by his persistent concern for the facts of motivation. It is, indeed, his unswerving devotion to fact, observation, and experiment that has given his contribution an integrity of inestimable value to scientific psychology."

There is no doubt that the investigations which Dr. Harlow undertook with the support of his Public Health Service research grants have been a major factor in the award of this citation.

PROJECTS WITH ODD TITLES

Mr. FOGARTY. There are also many project titles that people pick up and ridicule without ever finding out what the project is about—research on daffodils and things of that kind. Would you, for the record, pick out a few completed projects that had titles like this and give the worthwhile results that were obtained?

Dr. SHANNON. This we will be glad to do, sir.

(The information follows:)

SOME RESULTS DERIVED FROM STUDIES QUESTIONED ON THE BASIS OF TITLES

A STEREOTACTIC ATLAS OF THE BEAGLE BRAIN

It is now possible for medical scientists to pinpoint specific regions of the brain by external landmarks on the skull. Clinically this information is extremely important in neurosurgery and in the introduction of radioactivity or electrodes to regions of the brain. Scientifically it provides a new tool in manning the internal structures and regions of the brain.

The development and refinement of these techniques can only be done in animals, and the dog's skull is a particularly useful model.

The Public Health Service is supporting the development of a stereotactic atlas of the dog brain. The project is under the supervision of Dr. Nicholas Wetzel of the Northwestern University, Chicago, Ill. (PHS Grant No. B-2196). Such an atlas would enable investigators to use the same baselines in future research. A number of dog brains have been treated so as to provide information on the relation of internal brain structures and external landmarks. The data is being collated and readied for publication. This is a precise and exacting task involving the skills not only of the neuroanatomist but also artists, photomicrographers, and the duplication and printing of charts. It is expected that the atlas will be published within a year.

BEHAVIORAL AND PHYSIOLOGICAL CONCOMITANTS OF DREAMS

This study is being conducted by Joe Kamiya of Langley Porter Neuropsychiatric Institute, San Francisco, Calif., (PHS Grant M-5069).

Only in recent years has it become evident that dreaming may serve some very important psychological and physiological functions. Dreaming is normally universal and accounts for more than one-fifth of every night's sleep; recent studies of dream deprivation have shown that when dreams are interrupted by forced awakening or by administration of certain drugs, the individual later shows a number of psychological disturbances. For example, he develops feelings of anxiety and tension, and he displays mild memory disturbances and difficulty in concentration; some individuals deprived of dreaming also develop intense hunger. The importance of dreaming is also apparent from the fact that normal persons who are deprived of dreams for several nights, when finally allowed to sleep normally, experience an increased amount of dreaming—as if in an attempt to make up for the earlier lack of dreaming.

Research on dreaming is technically difficult, and until recently few investigators have studied the phenomenon. In the past 2 years, Dr. Kamiya has contributed substantially to the methodology available for studies of dreams, and he has added knowledge about the physiological and psychological processes associated with dreaming. Dr. Kamiya has produced more specific information than has hitherto been available about overall patterns of dreams and the relationship of sequences in the dream pattern to physiological changes—for example, in heart rate and respiration rate. His results have confirmed the important role which dreams and the sleep cycle play in the psychological as well as the physical health of the individual.

THE ORAL HEALTH OF ICELANDIC PEOPLE

By the age of 50 most of our population lose teeth because of periodontal disease. By age 65 almost all the population has suffered from this disease. It is painful, annoying, disabling—and expensive. By studying the incidence of the disease in its different manifestations in different peoples, with different foods, different climate, and different customs we may be in a position to make a sizable contribution to the health and pocketbook of the average American.

A study of the oral health of Icelandic people was undertaken by a University of Alabama team under the supervision of Dr. Joseph F. Volker, dean of the School of Dentistry and vice president in charge of health affairs. The study was supported by PHS Grant No. D-865. Dr. Volker has both a Ph. D. and a D.D.S. degree, and before heading the Alabama program was the dean of the College of Dentistry at Tufts University.

He and his coinvestigators are recognized as outstanding scholars and research scientists and have been deemed well-qualified to handle this project.

The facilities to carry out the work are recognized as excellent both in Iceland and in Alabama.

This study takes advantage of the opportunity to correlate many factors—climate, industry, population, drinking water, age, organization—and the relationship of these to the serious problems of tooth decay and oral disease. We can learn from these studies some of the mechanisms involved in cultural change related to oral problems and possibly how to protect our teeth.

The survey has already produced some significant reports presented at the meeting of the International Association for Dental Research, March 1962, and printed in Public Health Reports 77: 594, 1962. The investigators found a higher prevalence of tooth decay and gingivitis in children in Iceland than in those of other nations. The contrast with Alaska was marked. The high rate of gingivitis in children was particularly surprising since periodontal disease in youngsters has not heretofore been considered a significant area of study. If we can determine why the gums of small children in Iceland show disease when the supporting structures of the teeth of those in other countries do not, we may have a most important clue to the dental problem of our own older age groups.

INVESTIGATION OF INFORMATION CONTAINED IN ECHOS

It is recognized that the orientation and location of objects is a crucial detriment to useful life among the blind. Numerous attempts have been made to assist the blind in obstacle detection and orientation, but the basic methods by which the blind are able to find their way continue to be through the use of canes, guide dogs, and human guides.

The ability of bats to navigate, avoid obstacles, and apparently detect the form and shape of objects in the absence of light is well developed. A group of investigators from the University of Arizona under the leadership of Dr. Howard Baldwin (PHS grant No. B-2656) has designed a program to duplicate or simulate the physical apparatus used by bats in these processes.

The group's major effort has been spent in developing a miniature sound-generating system which could produce these sonic signals. Although some advancements have been made in reducing the size of certain electronic components, a practical model for use by the blind has not yet been developed.

STUDIES OF SILENT THINKING

Dr. Irving Maltzman of the University of California, Los Angeles, Calif., is conducting research (PHS grant No. N-4684) designed to gain insights into the thought processes of mentally disturbed persons, particularly **schizophrenics**. Mutism is a prime symptom in the pathology of schizophrenia, and one of the most difficult problems encountered in the study and treatment of the disorder is the patient's unwillingness or inability to say what he thinks or feels.

Dr. Maltzman has perfected a method for studying language and thought processes; the method is particularly adaptable for use with schizophrenics because it includes several physiological measures that can indicate the patient's reactions to words or ideas without his having to respond to them verbally, and it is in this sense that he is studying "silent thinking."

Using this method, Dr. Maltzman has conducted eight major studies in the areas of language and thinking. He has found significant differences between schizophrenic and normal persons in terms of their ability to learn and to respond to verbal material; furthermore, he has found differences between female and male schizophrenic patients. Dr. Maltzman's results to date indicate that the schizophrenic's facility with language, although generally lower than the normal person's, is not uniformly affected by his disorder; his responses are markedly different for highly personal words, for example, as compared with neutral words. Such findings carry important significance in the diagnosis and treatment of mental illness.

RED TUNA AND YELLOW FAT DISEASE IN THE CAT

Scientists everywhere are attempting to find a safe agent which would lower high blood cholesterol levels and would reduce the frequency of abnormal fat metabolism in man. Search for a safe drug of this kind is potentially of great importance to the problem of atherosclerosis. One biomedical research scientist, supported by the National Institute of Arthritis and Metabolic Diseases has reported encouraging results in a study related to the search for such an agent.

This scientist is Dr. Gordon W. Newell, of the Stanford Research Institute, Menlo Park, Calif., whose research project (PHS grant No. A-5194) bears the abstract and misleading title of "Red Tuna and Yellow Fat Disease in the Cat."

Red fish and yellow fat studies seem remote from research to reduce excessive blood cholesterol levels in man, but possible agents for accomplishing this reduction include certain fats found in fish oils. Large amounts of these fats which are highly "unsaturated" are contained in some ocean fish oils. However, before these substances can be used in medical experiments involving the reduction of excessive blood cholesterol levels in man, their safety or possible toxicity must also be investigated. This is important because an unusual disease in cats, "yellow fat disease" appears to stem from the toxic action of the fat found in certain species of red tuna. This happens only under special experimental conditions, namely, when the meat of these fish is the only food consumed by the cats.

In his present studies, Dr. Newell is attempting to find a way to protect cats fed these marine oils in large quantities, from yellow fat disease. It is possible that the use of antioxidants (substances which hinder oxidation) will overcome the toxic effects, permitting the special fat found in red tuna to be tested for its ability to lower cholesterol. Several antioxidants are being tested by Dr. Newell in an attempt to treat or prevent yellow fat disease in experimental animals, before any recommendation is made involving the use of these special red tuna oils by human subjects.

Early results obtained by Dr. Newell have shown that it is possible to inhibit yellow fat disease or keep it under control in many cases through the use of several antioxidants. This is an encouraging finding, and although preliminary, opens the way for further promising results.

Dr. Newell is also using the condition of yellow fat disease in the cat as a test situation which can help to determine what happens, and why, during the process of aging especially when aging is accompanied by longstanding abnormal fat metabolism. Among other manifestations, yellow fat disease causes a deposition within the cat's fatty tissues, of an abnormal fatlike substance called ceroid. The longer certain red tuna oils are fed to the cats the greater the accumulation and deposition of this ceroid. Moreover, this unusual fatty substance is highly insoluble, and once it is deposited in the animal's fat tissues, it is extremely difficult for the body's normal chemical processes to remove it.

Dr. Newell has found that ceroid which accumulated when he fed his cats red tuna marine oils in large quantities, is still present in their tissues for more than a year after the cats have been switched to a normal diet. He has also found that the special red tuna fats affect the formation or production of hemoglobin, the oxygen-carrying red pigment of blood. In advanced cases of yellow fat disease, the animals—fed exclusively on a diet of red tuna—were found to develop anemia. In this advanced condition, and especially during the terminal stage, the animals also showed typical paralytic symptoms. What Dr. Newell has found in this project is that certain antioxidants are able to inhibit yellow fat disease or keep it under control.

Dr. Newell has also observed that the ceroid material in his experimental animals appears to be very similar to the type of ceroid which accumulates during the aging process in man. He feels that the yellow fat disease in the cat thus could offer an important research tool for the investigation of an important factor involved in human aging.

In order to avoid any popular misunderstanding concerning the use of tuna meat in the feeding of cats, it is important to emphasize that long term studies by Dr. Newell have shown that ordinary tuna pet foods for cats, in contrast to the special experimental diets employed by him, are definitely nontoxic and will not cause "yellow fat disease" in cats.

PROJECTS CRITICIZED

Mr. FOGARTY. There were two or three projects criticized during debate on this bill last year. Would you also place in the record the details concerning these projects and the worthwhile results, if any?

Dr. SHANNON. Yes, sir.

(The information follows:)

STATUS OF PHS SUPPORTED RESEARCH PROJECTS DISCUSSED IN SUBCOMMITTEE HEARINGS AND ON THE FLOOR OF THE HOUSE OF REPRESENTATIVES IN CONNECTION WITH NIH APPROPRIATIONS FOR FISCAL YEAR 1963

STUDIES OF BODY TEMPERATURE REGULATING MECHANISMS

As previously reported, this study, which is being carried out by Dr. James D. Hardy, director of the John B. Pierce Foundation Laboratory, New Haven, Conn., under PHS grant No. B-3826, is based on the fact that the regulation of body temperature is one of the most important homeostatic mechanisms of warmblooded animals. In the human, prolonged body temperatures above 106° F. are incompatible with life. A change in body temperature is one of the prominent features of many infectious diseases. Recently, the use of lowered body temperature during anesthesia has proven a valuable aid to surgery. An exact knowledge of the temperature-regulating mechanism is essential to further refinement of this technique.

Newly developed techniques, especially those involving the use of microelectrodes in the brain, now make it possible for the first time to record the activity of nerve cells within the brain that are involved in the temperature regulating mechanisms. In addition, refinements of the methods for measuring heat exchange now make possible an exact correlation between the regulatory function being performed and the activity of the nervous system responsible.

There is some evidence that the hypothalamic area of the brain may be the part of the nervous system which controls body temperature. However, this has not been satisfactorily substantiated and needs further exploration. Also to be explained are the roles of the skin and deep thermal receptors in the regulation of body temperature, especially their relationships to the hypothalamic area of the brain. In an effort to answer these questions, the investigators are conducting studies in animals by studying the electrical activity of the individual nerve cells of the hypothalamic area of the brain. These are being studied in response to various localized and generalized experimental temperature changes, as well as the responses of the skin and deep thermal receptors to controlled temperature changes.

Preliminary findings derived from the initial year of this study reveal:

1. Experiments performed on patches of the camel's fur indicate that at least half of the heat is lost by means of reradiation reflection, and conduction.
2. Further heat loss is accomplished by the evaporation of water, which accounts for a substantial amount of heat loss.
3. Surplus heat, resulting from maximal thermal exposure, is stored by the animal during the day. By later afternoon, the temperature of the animal may rise to a point very close to 108° F.
4. During the cool of the night, this surplus heat is dissipated so that by morning the animal may reach a temperature of about 90° F.
5. Preliminary experiments have indicated that the temperature of the hypothalamus is lower than rectal or vaginal temperatures by about 2° F.

FUNCTIONS OF PLAY IN DEVELOPING ADULTHOOD

Dr. David Riesman of the University of Chicago, Chicago, Ill., has conducted the project based on the theory that the psychological development of the individual depends in large measure on the quality of his interpersonal relationships. The study was supported by PHS grant No. M-891. Although much attention and study have been devoted to family relationships such as those between parent and child, there has been very little research on the role of other social relationships in personality development. It was Dr. Riesman's hypothesis that the role of these other, less intimate, social relationships is an important one, since, for example, much of the psychological development of the child and

adolescent takes place in social situations. It is in such settings that different patterns of behavior are tried out, practiced, and found successful or unsuccessful. Results of such social experimentation are an important factor in shaping a person's subsequent personality development.

Dr. Riesman hypothesized that, since social activities are chosen voluntarily, such activities would be more likely to reflect an individual's personality than would his participation in nonvoluntary activities. In order to pursue his aims, he chose for study four different social situations. One was a study of close friendships, analyzing the ways they change in time and the influences they have on the personalities of the individuals involved. The second was a study of sociability patterns among professional people and the effects of such patterns on the individual's perception of his professional role. The third study was an analysis of the psychological effects of participation in a social function on the persons attending it. The fourth study, an investigation of social interaction patterns of college students working at a summer camp, focused on the relationships between an individual's social experiences and his level of psychological maturity.

The results of his analyses indicate that the dramatic social and economic changes which have occurred in this country in the past three decades have been accompanied by distinctly different forms of social interaction. Greater economic and social security has resulted, for example, in more time and money to devote to leisure time and social activities.

Dr. Riesman found, however, that the social interactions developed during these leisure time hours are more for the purpose of sharing mutual anxieties than they are on the development of personal resources. For example, one major function of a modern social group is to derive explanations and interpretations of an often complex and bewildering society; the explanations and interpretations secured are usually those which give maximum self-esteem and protection to group members.

Riesman also found that an individual who is going through a period of transition in his life uses a social group situation to obtain reassurances from others about his own importance and self-esteem; this situation is typified by the college student who is breaking away from one family and preparing to establish another. Individuals who spend a majority of time and energy in occupational roles which contribute little to their sense of personal worth also develop social relationships for the purpose of enhancing their feeling of self-esteem and importance.

A TEST OF THE HUSBAND-WIFE RELATIONSHIP

This study is being conducted by Uriel G. Foa, of the Israel Institute of Applied Social Research, Jerusalem, Israel (PHS grant No. M-2669).

The purpose of Dr. Foa's research has been to provide a more detailed analysis than is now available of the complex psychological factors that affect the relationship between two individuals. More specifically, he has sought to produce new understanding of the ways in which individuals misperceive and distort one another's feelings and behavior. Such an understanding is of considerable importance in mental health; accurate perceptions by two individuals of each other's feelings and behavior are critical in personal adjustment and stability.

Dr. Foa is focusing on one of the most important human relationships—the relationship between husband and wife. Because marital problems often arise out of a misunderstanding by one partner of the other's feelings, Dr. Foa's results have important implications for the creation of an emotionally healthy family atmosphere which, in turn, is crucial to the normal psychological development of children.

Dr. Foa has developed a testing technique which reveals the existence of distorted ideas on the part of one marital partner of the other partner's attitudes and feelings. The testing technique allows objective scoring—thus providing a reliable instrument for assessing personality problems that interfere in interpersonal relationships. The test involves the use of pictures showing problem situations between husband and wife; these pictures elicit the individual's feelings and ideas about his marriage, himself, and his spouse.

An objective test of the type developed by Dr. Foa carries great potential for use in marriage counseling services, and may also be applied in more general diagnostic and psychotherapeutic settings; the test can also serve as a useful tool for other, comparable research investigations.

NUTRITIONAL TEAMS ABROAD

The nutritional teams that have gone abroad have been sent by the Interdepartmental Committee on Nutrition for National Defense which was organized in 1955 and is formed by representatives from the Departments of State; Health, Education, and Welfare; Defense; Agriculture; the Agency for International Development; and the Atomic Energy Commission. The Secretariat of the ICNND is located on the campus of the National Institutes of Health and operates administratively through the National Institute of Arthritis and Metabolic Diseases.

The international responsibilities of this Institute in nutrition research were incorporated into the Institute at its formation and have for their basic purpose the accumulation of fundamental scientific data directly related to our understanding of diseases of importance to the health of the people of the United States.

Following an official request from the country concerned, transmitted through State Department channels, the ICNND and the government of the host country organize a team of nutrition scientists from the laboratories and universities of both countries (usually about 15 Americans and two to three times this number from the host country). This team then undertakes an extensive survey of each aspect of nutrition throughout the country, from which results a detailed scientific report both in English and the national language, with recommendations centering about self-help programs designed to improve the nutritional status of the local population. Every effort is made to coordinate recommendations with existing and envisioned programs of the host country and the United States.

The activities and accomplishments of the ICNND were reported to this committee during hearings on fiscal year 1963 appropriations for the National Institute of Arthritis and Metabolic Diseases and were published in the hearings. Since that time, four additional surveys have been made, one each in Uruguay, Jordan, Bolivia, and Malaya.

COST INCREASES

Mr. FOGARTY. We will place in the record at the end of this discussion, the various tables and statements you have prepared at the request of the committee. Will you also prepare a table showing by Institute all the mandatory increases in costs in 1964, including increases budgeted for overhead?

Dr. SHANNON. Yes, sir.

(The information follows:)

Mandatory increases, 1964 President's budget

[In thousands of dollars]

	GRS-NIH	Biologics stand-ards	Cancer	Mental	Heart	Dental	Arthritis	Allergy	Neurology	Management fund	Total
1. Annualization of new positions authorized in 1963.....	157.0	95	179	140	136	42.8	154	20	408	137	1,468.8
2. Annualization of commissioned officers quarters allowance.....	1.3	5	24	56	22	8.0	17	35	10	24	1,202.3
3. 2 additional days of pay in 1964.....	22.0	12	64	54	43	12.0	34	33	33	188	495.0
4. Pay increase.....	113.0	68	273	255	149	52.0	149	124	182	559	1,924.0
5. Additional indirect costs:											
(a) At 20 percent.....	2,424.0	0	2,317	2,434	3,676	364.0	3,126	1,515	2,204	0	18,060.0
(b) At 25 percent.....	805.0	0	774	808	1,220	120.0	1,038	503	732	0	6,000.0
Total.....	3,522.3	180	3,631	3,747	5,246	598.8	4,518	2,230	3,569	908	28,150.1

ARTIFICIAL KIDNEY CENTERS

Mr. FOGARTY. We have a letter from an official of the Izaak Walton League of America addressed to me, January 29, 1963.

DEAR CONGRESSMAN FOGARTY: I wish to invite your attention to a most serious deficiency in the medical service of our country. I refer to the lack of kidney centers where people can be kept alive indefinitely despite a total loss of the kidney function.

At the Swedish Hospital in Seattle, Wash., there exists a highly trained team of experts, equipped with a kidney simulator, that are keeping alive on a continuing basis a carefully selected group of 11 persons who have lost the kidney function entirely. I understand that this is the only group of its kind. A very dear friend of ours was selected as one of the 11. But for the existence of this highly specialized team of dedicated medical experts supported, in large part at least, by the Hartford Foundation of New York, these 11 persons would not be alive today. Others, how many I do not know, are dying for lack of comparable kidney centers. I'm told that such centers are needed in every large city throughout the Nation. Private funds are being urgently solicited to extend this lifesaving medical service.

But, Congressman Fogarty, is it not possible for medical appropriations of the Congress for medical research and care to be used for saving the lives of such kidney sufferers? We spend millions of dollars of Government and private funds, and rightly so, to find out how to save cancer victims. In the case of the kidney ailment, we know, after trial and error, not without tragic experience, how to save victims but, with a single exception, we are not doing anything about it.

I read in "Science" recently that the Congress appropriated about \$880 million to the National Institutes of Health last year (\$100 million more than was requested)—surely a generous allotment. It comes to mind, therefore, that your subcommittee may wish to investigate the nature of the need for establishing lifesaving kidney centers throughout the Nation as a basis for earmarking adequate funds to remove this great national medical deficiency.

Thank you for whatever attention you and your committee members may be able to give my request. I presume that others have written to you on behalf of this crying need for medical care. So I am happy to join them and all sufferers from this critical disease in pledging deep appreciation for any assistance, however small, that may be forthcoming.

This is from Curtis L. Newcombe, first vice president, California State Division, Izaak Walton League of America.

He sent copies to Lister Hill, John Baldwin, and Don Magnuson.

Dr. SHANNON. Mr. Fogarty, this is a technique that was developed with our support at the University of Washington by Dr. Scribner. It is possible with the devices developed to use artificial kidneys as a lifesaving measuring in a substantial number of individuals. About a year ago Dr. Scribner requested a very substantial increase into research support that would enable him to increase the number of people that he was assisting with these machines. NIH support was the result of the judgment that the research was good and that development of it in terms of converting it to a practical tool was also an appropriate responsibility.

However, the making available of the device developed for the routine care of patients was not an NIH responsibility. We prepared a very definitive report in this matter and transmitted it to Dr. Terry, pointing out that here was a problem that the Bureau of Community Services should look into from the standpoint of whether or not they should concern themselves with the possibility of making these devices available on a wider base than the Seattle area. I pointed out that this is one of a number of advanced therapeutic techniques that were extraordinarily costly but nonetheless extraordinarily effective and

suggest he might wish to discuss it with the Secretary to try to arrive at a general policy as to what the role of the Department should be in making such devices and techniques available.

I know that preliminary discussions have been undertaken. We would be glad to make available to you the substance of the report we made to Dr. Terry.

Mr. FOGARTY. Please do that and we will place it in the record at this point.

(The information referred to follows:)

STATEMENT REGARDING ARTIFICIAL KIDNEY CENTERS

(Report by the National Institutes of Health to the Surgeon General)

A difficult situation has arisen as a result of the success achieved by Dr. Belding H. Scribner in Seattle in the management of patients with terminal uremia attributable to irreversible chronic renal disease. Useful lives of such patients are being prolonged by a new technique of hemodialysis providing ready access to the patient's circulatory system through insertion of indwelling plastic valves in the blood vessels of the patient's forearm or abdominal wall. This allows frequent and easy attachment of the patient to an artificial kidney. Lives of some patients have been prolonged for 2 years, most of them are gainfully employed. The crux of the problem which has arisen is the disparity between resources and needs. At this time, the cost of treatment for patients of this character is probably not less than \$10,000 and may be as high as \$50,000 per year; and as many as 10,000 patients might derive benefit from the therapeutic procedure. The resource requirement becomes the more staggering when it is recognized that periodic dialysis, to the extent that it is successful, becomes a modality of therapy on which the patient is completely dependent for the rest of his life. Aside from Dr. Scribner's unit in Seattle, which can handle a maximum of about 50 patients, there is no other unit engaged in this activity at the moment.

In view of the disparity between needs and resources, Dr. Scribner has been confronted with a situation in which the number of patients eligible for treatment, by even the most rigid medical criteria for acceptability, far exceeds the resources. He has dealt with this intolerable reality by establishing a procedural mechanism through which patients he considers acceptable are referred for final selection to a board of community leaders whose criteria are essentially social.

It appears that society in general is faced with a very serious challenge in this matter. Many individuals, whose lives could be significantly prolonged, are now destined to die because adequate resources and facilities for their treatment do not exist. The situation has received national publicity and it is reasonable to anticipate that this publicity will generate interest and requests for some sort of action. A response minimally appropriate to the need will be enormously expensive and it can be anticipated that there may be requests to make the problem the responsibility of some agency of the Federal Government.

The NIH is currently providing Dr. Scribner with support for research essential to the establishment of criteria for selection of patients, but the adoption of this or similar methods in treatment of patients is beyond the scope of our mission.

Against this background information and particularly in view of the fact that national publicity is being given the matter, it would seem important that the Public Health Service give thoughtful consideration to the preparation of a position it might take if and when we are called upon for such.

PERIODIC HEMODIALYSIS IN CHRONIC UREMIA

(Statement by Community Health)

The development by Dr. Belding H. Scribner of a kidney dialysis method whereby persons with irreversible kidney failure (chronic uremia) may lead fairly normal productive lives for a period of years after they otherwise would have died, presents a difficult problem. The problem grows primarily out of the large potential cost of providing the necessary treatment. If the present outlook is correct, this cost almost certainly could not be met without substantial Federal assistance.

Dr. Scribner's method (appendix A) involves attaching the patient to an artificial kidney machine twice a week for about 12 hours. Attachment is made through a plastic coupling which is permanently inserted in an artery and vein, thereby eliminating the need for surgery and the destruction of a blood vessel each time. Between dialyses, the patient must follow a strict diet and protect the plastic coupling in his arm, but otherwise need not seriously restrict his activities.

In addition to being applied by Dr. Scribner at the University of Washington teaching hospital, the long-term periodic hemodialysis method has been carried out under the supervision of Dr. John S. Murray at Swedish Hospital in Seattle. So far only about a dozen patients have been treated. However, in almost every case the method has proved successful in maintaining reasonably productive life (appendix B).

Because the number of people in this area needing treatment far exceeds the capacity of the treatment source, patients have had to be selected on the basis of their general worthiness as well as their medical suitability. The moral problems involved in such life-or-death choices receives attention in the Life article (issue of Nov. 9, 1962: 102-125).

Leading kidney specialists generally believe that periodic hemodialysis, although still in the developmental stage, could be successfully applied to some 2,000 new victims of chronic uremic failure a year, or a total of 10,000 persons by the end of 5 years. This includes all physically strong and emotionally mature patients having kidney disease in fairly pure form uncomplicated by hypertension or other afflictions.

At an estimated minimum cost of about \$8,000 to \$10,000 per patient per year, the total annual expense for treatment of 10,000 patients would be on the order of \$80 to \$100 million. The patient load probably would become greater than 10,000 in future years. Average life expectancy of patients might prove to be more than 5 years. With refinements in treatment, the types of patients accepted for care might be extended to include children, persons over 45 years old, and others now deemed ineligible. The increase in the general population alone would tend to increase the annual additional number of persons needing treatment.

Breakthroughs in the prevention of chronic kidney disease apparently are not imminent. Nor do alternative forms of treatment such as kidney transplantation and peritoneal dialysis show promise of being widely applicable within the next few years. It would probably be a mistake to plan on the assumption that periodic hemodialysis would soon become unnecessary or outmoded. The method itself might be perfected, of course.

The cost of long-term hemodialysis is not likely to fall at an early date beneath the estimated \$8,000 to \$10,000 per patient per year. Staff needs now account for the bulk of the cost. Although such devices as disposable dialysis units might allow some reductions in staff time, the process of dialysis already has been automated to a higher degree. The \$8,000 to \$10,000 estimate already assumes substantial savings under past experimental costs.

The heavy cost of care per patient would be offset at least in part by the economic contribution made by the patient—in his job and in supporting any dependents. But the problem of how to raise the money to provide the care would remain. At present levels of expense, it would be a rare patient who could pay the full cost of his own care, especially after several years of treatment.

To expect private sources to make available any large percentage of the total funds required annually for care of chronic uremia patients probably is unrealistic. State and local governments doubtless could play some role in supporting long-term periodic dialysis treatment. But limitations on this source of funds must be recognized.

The National Institutes of Health have given substantial support for the research done by Dr. Scribner in the development of his method of treatment. There is some question, however, whether further developmental work can be justified as research.

Other existing Federal programs might give limited aid for additional application of periodic hemodialysis. Community Health Services project grants, now at the \$7 million level, but with an authorization of \$10 million could be used in developing the program by training and demonstration projects in periodic

hemodialysis in three or four selected areas of the country. Some aid for facilities might be available under the Hill-Burton program or the research facilities construction program.

Early establishment of a few additional treatment centers would have several advantages. The periodic dialysis method could be further tested for effectiveness—although past experience suggests that success in treatment would be virtually assured. Staff could be trained. The efficiency of the method might be improved, and its cost possibly reduced. Such centers could also conduct additional research on peritoneal dialysis, kidney transplants, and other possible alternative methods of treatment.

In the absence of any Federal aid, a few additional treatment centers probably would be created, using voluntary and other non-Federal sources of funds. By focusing public attention on the treatment, they would tend to create additional awareness of the need for provision of facilities to care for a larger number of patients.

APPENDIX A

DESCRIPTION OF THE METHOD OF HEMODIALYSIS

Hemodialysis is a process which involves the clearing of the bloodstream of its waste products. This is basically the normal function of the kidney. It can be accomplished with an artificial kidney, peritoneal filtration (peritoneal dialysis), or by transplantation of a kidney. The method used by Dr. Scribner and his group is by means of an artificial kidney.

The major contribution that the Scribner group has developed consists of a new cannulation technique in which the cannula in the artery is connected by shunt to the cannula in the vein. The shunt allows the blood to flow rapidly through the system and clotting is thereby prevented. Hemodialysis is performed as needed (usually weekly or semweekly) by replacing the shunt with the hemodialyzer circuit. Another difference is the use of a pumpless low temperature hemodialysis system which gives better dialysis.

All patients have indwelling arteriovenous teflon cannulas which are shunted when not used for hemodialysis. The four new patients at the Swedish hospital have cannulas made of silastic and teflon. The original patients have more recently changed to silastic-teflon cannulas.

The composition of the dialysate is determined on the basis of the anticipated need to remove extracellular fluid and potassium.

The hemodialysis is supervised by a nurse. The physician's duties are limited to obtaining an interval history, doing a brief physical examination and writing orders. When there are occasional problems with dialysis which the nurse feels she cannot handle, a physician is called.

The patients live at home and enter the hospital approximately 1 hour before the time of each scheduled dialysis. The dialysis usually lasts 8 to 12 hours.

The criteria used at the Swedish Hospital, Seattle, for the choice of patients are the following:

- (1) A stable, emotionally mature adult under the age of 45 who is disabled by symptoms of uremia.
- (2) Absence of long-standing hypertension and permanent complications therefrom, particularly coronary artery disease and cerebrovascular or peripheral vascular disease.
- (3) Demonstrated willingness to cooperate in carrying out the prescribed medical treatment, especially the dietary restrictions.
- (4) Renal function should be stable or deteriorating slowly since any residual functions simplifies the therapeutic problem.
- (5) Children and young adults who are not potentially self-supporting have been excluded, so far.

The final choice is made by a seven-member group composed of citizens.

APPENDIX B

PRESENT STATUS OF PATIENTS ON HEMODIALYSIS

At the present time, the seven patients who are on hemodialysis in Seattle are being cared for at the unit in the Swedish Hospital of Seattle. This unit is financed by the Hartford Foundation. The money for continuation of this

unit supplied by the Hartford Foundation will terminate in July 1963. Three of the seven cases came from the University of Washington unit.

A summary as of December 14, 1962, of the status of the seven patients follows:

"One patient has been in the unit 16 months, two patients 15 months, one patient 10 months, two patients 3 months, and one patient 2 weeks. No patients have been lost in this unit (in the University of Washington unit one patient died of coronary occlusion in 1961). All the original catheters are still in place with no indication of infection or difficulty with the catheter. Six of the seven patients are at full duty gainfully employed and carrying on a normal life. The seventh patient has been in the unit for 2 weeks only, which makes it impossible to evaluate his present status."

It is the feeling of persons who have made site visits to the unit that with the techniques developed here, the same type of result could be achieved in other parts of the country if funds were available.

Mr. FOGARTY. All right. Is there anything else you want to say?

Dr. SHANNON. No, sir.

Mr. FOGARTY. We will recess until 10 tomorrow morning.

FRIDAY, MARCH 8, 1963.

Mr. FOGARTY. The committee will come to order.

Mr. Laird.

BASIL O'CONNOR SPEECH

Mr. LAIRD. Dr. Shannon, my senior Senator, William Proxmire, has, on several occasions, placed certain statements about the activities of the National Health Institutes in the Congressional Record. I am particularly interested, at the moment, in the speech which he made on January 23, 1963, under the heading: "O'Connor criticizes waste in Government-supported scientific research."

The chairman of the committee yesterday asked about certain statements contained in the speech of Basil O'Connor, which was made in La Jolla, Calif.

Have you had an opportunity to go over the Congressional Record of January 23, 1963, in which this speech was inserted?

Dr. SHANNON. Mr. Laird, I have. I read it very shortly after it was prepared by Mr. Proxmire, and had previously seen a copy of Mr. O'Connor's speech on which Mr. Proxmire's comment was based.

Mr. LAIRD. Are you going to discuss this in some detail?

Dr. SHANNON. Mr. Laird, we did discuss it briefly in terms of quite generalities of the issues raised yesterday afternoon.

I might say that, quite apart from that, we do not agree with a considerable amount of material presented by Mr. O'Connor in his basic speech and we had prepared materials for the Public Health Service and for the Department to comment on the items that were raised.

This we will be glad to make available to you, if you wish.

I cannot recall the specific issues from memory now, this has been about a month and a half ago.

Mr. LAIRD. Well, I wonder if that could be placed in the record at this point.

Mr. FOGARTY. I did ask, yesterday, that a statement be prepared on this subject to cover it completely.

Dr. SHANNON. We were distressed with some of the things Mr. O'Connor said, because of his long attachment in medical research, his

long contact with the support of science. We felt that some of the statements, or some of the positions he took were not well taken, and yet we are not in a very good position to enter into open controversy with individual citizens who care to criticize the overall area of our activity.

Mr. LAIRD. I think though, this committee should have the facts relating to the charges that were made.

Dr. SHANNON. We would be glad to make a factual analysis available.

Mr. FOGARTY. All right.

Mr. LAIRD. That is all I have.

(The information supplied follows:)

COMMENTS ON THE SPEECH "SCIENCE AND GOVERNMENT, THE PERILOUS PARTNERSHIP," DELIVERED JANUARY 16, 1963, BY BASIL O'CONNOR, PRESIDENT, THE NATIONAL FOUNDATION, AT THE THIRD INTERNATIONAL SYMPOSIUM ON IMMUNOPATHOLOGY, LA JOLLA, CALIF.

The thesis

The address by Mr. O'Connor in essence sets forth the following thesis:

Largely as a post-World War II phenomenon, science and government have become mutually dependent (only science can provide government with the new knowledge and technology essential to survival; science depends on government for a growing portion of its support). Mutual government-science dependence (though it has hopeful features) constitutes a present danger to science, because (1) money tends to substitute for intelligence, with resulting loss of scientific excellence and even of progress, and (2) the good name of science can be degraded by the "scientific logrolling and sheer waste which accompany ill-advised massive government appropriations." The area of biomedical research is singled out to illustrate this thesis.

Mr. O'Connor acknowledges the controversial character of the matters he discusses and states that his objective in speaking is to obtain realistic appraisal of these problems as a basis for intelligent action.

The general considerations

Before considering the specific criticisms set forth in support of this basic thesis, three general considerations relating to the viewpoint reflected by Mr. O'Connor should be noted:

1. The concern is with attributes (source of support, potential threats, and dangers to scientists and universities, nature of the advisory process, etc.) rather than the substance of what has taken place through federally supported research programs (changes in the substance of the biosciences, results of scientific effort, qualitative character of graduate education in the biomedical sciences, etc.).

2. The approach to and attitude of the presentation is pessimistic. The issues are discussed in terms of alarms, dangers, forebodings, and personal apprehensions over what are depicted as deteriorating trends in the general scientific scene and particularly the medical research scene by virtue of increasing Federal support of these activities. There is no documentation of what, in fact, has been the changes brought about by such support nor any scientific assessment of their qualitative character. Thus the pessimism expressed would appear to reflect more a nostalgia for a past setting than a recognition of the true nature of the current scene.

3. The criticisms made do not appear to recognize the fundamental difference between the role of Government and the role of private agencies in the support of research. The governmental role inevitably and quite properly derives from a national decision to achieve certain major purposes in the interest of the common welfare. The magnitude and direction of effort put forth is basically related to the urgency and difficultness of the problems to be dealt with and the firmness of the national intention to obtain progress in respect to them. Thus the stubborn and intractable problems cannot be avoided, the dimension of attack must be commensurate with the objective, and considerations of excellence must be related to what can, and must be done, rather than an abstract concept sought solely for

its own virtue. In contrast, the objectives and character of the research support activities of private agencies are quite properly and usefully different. The nature of such programs is a private, not a public choice deriving from the diversity of private motivations and interest. Excellence can be sought for its own sake, not as an attribute of a necessary activity. The magnitude of effort is a consequence of the accidental circumstances of private philanthropy and charity, rather than a measure of need, urgency, and national determination. Thus private and governmental efforts in support of science serve different rather than competitive purposes. Private activity cannot hope to meet the full measure of national needs and purposes in science, but its emphasis on excellence and diversity has a pervading influence of significant value. Governmental activity, on the other hand, must meet the national requirements through a concentration of effort where excellence is the prime but not the sole consideration.

To illustrate further the fundamental questions involved in this last point, it is useful to look first at the philosophy and experience of the great private American foundations. Since about 1900 the private foundations have served a unique purpose in American life, and particularly in the stimulation of science in higher learning generally.

This has been done, most notably by the Rockefeller Foundation, by the most scrupulous and exacting attention to the quality of individuals and institutions to whom awards are made. This philosophy of excellence has played a large part in the emergence of the United States as a major scientific power. It has literally created some institutions and strengthened many others for learning and teaching at the highest levels of excellence. One cannot praise too strongly the part which this philosophy of excellence has played in affecting the entire tone of the American scientific scene. As one specific example one can mention the success of the scientific fellowship program financed by the Rockefeller Foundation and administered by the National Academy of Sciences, particularly during the decade 1920 to 1930.

This philosophy of selection of excellence and concentration upon a limited group of institutions and individuals competent to exercise leadership and intellectual dominance lies at the heart of Mr. O'Connor's thesis. One cannot but have great sympathy for this viewpoint in view of its demonstrated effectiveness.

When one considers the role of government, as contrasted with that of private organizations, in the support of science and in the production of new scientists, one is forced, however, to reconsider most carefully whether there are any fundamental differences between the function of government and the function of private groups. There are differences, and these differences go to the heart of the distinction between the private and governmental roles and policies. Perhaps the most fundamental distinction between the role of government and that of private bodies is that government must pay attention not only to the top of the pyramid of scientific activity, but to the entire base required to support the pinnacle of scientific excellence. To the extent that the Federal Government, as determined by Congress, has a role in support of science and in the support of education for science, this role extends beyond the selection of the most eminent investigators and the most talented students. There are scientific tasks of great importance which inevitably must be carried out in institutions other than those of the highest scientific rank. Similarly, the advance of science and the full exploitation of the great intellectual advances in science require the development of a large number of scientifically competent individuals. Government is responsible for this layer of science as well as the topmost layer of highest excellence.

Viewed from what one might call the perspective of the private foundations, a governmental effort which extends beyond the points of highest scientific eminence can be caricatured as support of mediocrity by government and as a waste of money. If one accepts as the sole satisfactory basis for national action a philosophy that only a limited number of institutions and individuals of highest excellence should be supported, then it follows that broader support involving institutions and individuals of lesser eminence can be viewed as a disparagement and thus wasteful.

Conversely, if one accepts the philosophy that the role of government must extend to support of the entire base required to produce a strong structure of science for the Nation in the achievement of public purposes, then the philosophy of restriction to support of excellence alone is inadequate as a sole guide to public policy and action in this area.

The discussion of the specific criticism contained in Mr. O'Connor's address is rendered difficult since for the most part they are expressions of opinions about matters concerning which there are opposite but equally appropriate opinions of no less probable validity. Consequently the following basically reflects another opinion of these matters plus the correction of certain misstatements or overstatements present in the address.

Analysis of the specific criticism made by Mr. O'Connor

Mr. O'Connor has questioned the appropriateness of the Federal Government assuming primary responsibility for the support of medical research.

There are many people who question the growth of Federal expenditures in almost any area of activity. It is true that Federal support for medical and health-related research has grown steadily since 1947. It has grown largely because of the great needs of our people, the demonstrated capabilities of science to improve the well-being of man, and to contribute significantly to the attack upon disease, suffering, and human misery that accompanies disease.

The central question is not whether the Federal Government provides 10 percent of the funds, 50 percent of the funds, or 75 percent of the funds expended for medical research, but whether the funds provided are adequate and sufficient to take advantage of our growing research capabilities, to exploit the opportunities presented, and commensurate with the urgency and significance of the problems to be solved. It is extremely pertinent to note that non-Federal sources of support for medical and health-related research, despite their relative change in position, have continued to grow steadily year by year over the past 15 years and that this growth has apparently in no way been deterred by the fact that Federal funds have expanded.

Contrary to Mr. O'Connor's statements that the growth of Federal support is drying up all of the sources, expenditures for medical research from foundations, from voluntary health agencies, from State governments, from industry, from other private sources have in fact continued to grow and to grow steadily. In 1957 when NIH funds for support of research began a rather sharp upswing, there was concern over the possibility that there would be a drop in research support from other sources and particularly, that the voluntary health agencies would suffer. This has not occurred. Expenditures in this area by foundations, by voluntary health agencies, by State government, by industry, and from other private sources have, in fact, continued to grow and grow steadily in the postwar period. The following data show this:

Private support—Medical research expenditures

[In millions of dollars]

Source	1947	1957	1962
Total.....	60	201	479
Industry.....	35	126	345
Foundations.....	15	19	42
Health agencies.....		23	35
Endowment.....		19	19
Other private.....	(1)	14	38

¹ Not available.

Mr. O'Connor and others charge that the rate of growth of Federal support for medical research has been excessive.

On the contrary, congressional support has made it possible for PHS to develop a well-balanced program, extending across the entire range of diseases and including a solid foundation of fundamental research. The increase in funds has made it possible to balance support for today's research with the necessary effort to strengthen the research environment and capability of institutions and enlarge the resources in manpower and facilities for the future. Thus, the rate of growth has been quite adequate, and it has coincided generally with the overall growth of Federal support for science.

Mr. O'Connor makes the statement that "the National Institutes of Health are among the few Federal agencies which regularly receive more than the administration has asked for on their behalf from Congress."

While this statement may be true it is difficult to comprehend what is necessarily wrong with the fact of such a happening. A well-constructed budget is inevitably a series of compromises among many compelling but competing interests. As such, a national budget rarely pleases everybody nor does it necessarily establish the only measure of meaningful national action. It is the nature of our Government that the budget plans and proposals of the executive branch must be submitted for appropriation action to the Congress. The Congress is obligated to make its own independent assessment of such proposals and act upon them in terms of the congressional consensus of what the distribution of national effort should be. The area of medical research is by no means the only area of national policy and interest where there is a difference between the views of the executive versus those of the legislative. The existence of such a difference does not mean that one is right and the other wrong; it is reflective of the essence of our democratic process.

Mr. O'Connor compares the grant approval rates of NIH and the National Science Foundation with the implication that NIH appears to be much more lenient than NSF.

The statistics cited are in error, and this error has already been given unduly wide circulation. Mr. O'Connor states that NIH "gave 95 cents on the dollar to two-thirds of all new applicants." The correct figures for 1961 are these: NIH paid 45 cents on the dollar to 56.1 percent of all new applications. We do not have definitive figures yet for fiscal year 1962, but there are indications that the approval rate by NIH will be even lower for this more recent period.

There is a further matter that points out the lack of validity in comparisons of approval rates between NIH and NSF: It is this: Amounts awarded by NIH are for 1 year only. Even though support may be recommended for additional years, an additional award process is required for each year. On the other hand, if an applicant for an NSF grant requests support to cover 2 years or 5 years, etc., the initial award is intended to cover the full period approved. It is only reasonable to expect that a single award to cover, say, a 5-year period, will show a more dramatic reduction in percentage of total funds approved than one would expect to note in an approval to cover the first year only. The point is that the differences in grant approval methods used by NIH and NSF makes comparisons of approval rates between these agencies misleading.

In his speech, Mr. O'Connor expressed grave concern that scientific freedom was being endangered because of its dependence upon Federal support. He argued that science has traditionally maintained its independence by relying on diverse sources of support.

There is general agreement that diverse sources of support provide a substantial measure of protection for scientific freedom; they insure that the scientist will have access to support for his ideas, if they are good ideas, from a wide variety of sources involving different interests and methods of operation, rather than making him totally dependent upon the program interests and the terms of support of a single source. However, scientific freedom is not now or in the foreseeable future endangered by the present pattern of support for medical research.

First of all, the National Institutes of Health is by no means the only Federal agency providing support for medical research. Other Federal agencies such as the Atomic Energy Commission, the National Science Foundation, Veterans' Administration, the Department of Agriculture, the Defense Department, and increasingly, the National Aeronautics and Space Administration also provide support for medical research. Thus, within the Federal Government there are a variety of sources of support each quite different in program interest and terms and conditions of operation.

While it is true that Federal support has risen as a proportion of total national expenditures for medical research, all other sources have also continued to rise in amounts spent. Industry expenditures have risen steadily, State government expenditures for medical research through their health agencies, mental health agencies and great State universities have also expanded markedly, and foundation expenditures for medical research have increased steadily. The same is true for research expenditures of the voluntary health agencies, including the National Foundation of which Mr. O'Connor is the president. As a matter of fact, medical research stands alone among all the fields of science as the one area characterized by diversity rather than virtually total reliance upon the Federal Government. It is this circumstance that gives confidence that investigators in the health sciences are in little danger of losing their freedom.

Mr. O'Connor expresses great concern that Federal support for medical research may deprive educational institutions of their autonomy and divert them from their central purpose. While danger exists, in the administration of Public Health Service programs, everything possible has been done to assure that support for medical research will simultaneously strengthen our Nation's educational institutions. This has been done in many ways with a clear recognition that an agency responsible for the support of research must also concern itself with strengthening the environment within which research takes place and with enlargement of resources for the future. Thus, in addition to support of ongoing research, NIH programs provide for increasing the research and training capability of institutions through the creation of specialized research resources such as facilities for clinical research, for computing and data processing and animal research.

Furthermore, Public Law 798 enacted by the 86th Congress gives the Surgeon General authority to make grants for the general support of institutional programs of research and research training in the health sciences. These funds may be used by the institutions in the light of their best judgment of how their own capabilities and objectives in respect to research and research training can best be served. This activity has been undertaken with due deliberation, following extensive consultation with the scientific and academic communities to make certain that it did, indeed, serve institutional needs. In the current year this program is funded at \$30 million, roughly 7 percent of the amount requested for research projects.

To assure that NIH programs do strengthen the academic environment, great care must continuously be exercised so that the terms and conditions under which medical research is supported facilitate this objective. In this connection, the recent report of the Council on Medical Education and Hospitals of the American Medical Association is most gratifying. After an extensive study the AMA council concluded that added funds from research and research training programs have without question strengthened the faculties of our Nation's medical schools. The report also pointed to deficiencies but indicated that in the main, National Institutes of Health programs in the research and research training area have been highly productive.

These deficiencies were not the same as those alleged by Mr. O'Connor. Essentially, the AMA was concerned with the need for more substantial support, particularly support for the construction of teaching facilities and support to meet operating expenses of medical schools. These deficiencies, of course, lie outside statutory authority of the Public Health Service at the present time. H.R. 12 would go a long way toward remedying the present situation in which Federal funds are available for the support of research facilities and for the construction of hospitals but are not available for the support of teaching facilities in the health profession. However, H.R. 12 does not include provision for operating funds.

Mr. O'Connor refers to the fact that congressional appropriations have quite consistently exceeded the administration budget. He goes on to state that this congressional action has led to what he alleges to be "waste on a grand scale." He further alleges that the National Institutes of Health has felt itself under pressure to spend all of the funds appropriated to prevent their reverting to the Treasury.

These allegations are simply not true. In respect to the statement that NIH attempts to spend all of its money regardless of need simply to prevent funds from lapsing back to the Treasury, the NIH feels under no compulsion to spend funds unwisely merely in order to consume the amount that the Congress has authorized. The record will show the NIH quite consistently has returned some portion of the funds available to it for obligation to the Treasury each year. In fiscal year 1962 this amounted to \$71 million. The reasons for this are various but a major consideration is the fact that delays in the appropriation and apportionment process reduce the effective time to plan and execute a full fiscal year's program to a period which has often been less than 9 months.

Thus the fact that funds frequently do not become available until a substantial portion of a fiscal year has passed makes it difficult to program expenditures in conformance with NIH's high standards. When confronted with this problem, there is only one alternative, namely, not to spend that which cannot be spent wisely.

Mr. O'Connor in his charge of "waste on a grand scale" cited no proofs whatsoever. As a matter of fact, Mr. O'Connor doesn't make the charge even as a matter of his own opinion; he states that "waste on a grand scale" is what Abraham Flexner would find.

If Mr. O'Connor has reference to Dr. Flexner's Study of Medical Education early in this century, and if Dr. Flexner were to repeat his review today he would be impressed by these things:

He would find a vigorous and productive array of research and scientific institutions in the medical field;

He would find the whole process of medical education enveloped in an atmosphere of scientific creativity and experimental endeavor;

He would find more full-time faculty in medical schools than would have seemed conceivable before World War I;

He would find medical schools an integral and highly respected part of our higher educational setting.

He would find these schools far transcending their earlier limited role in training undergraduates as physicians but encompassing education in the full spectrum of the health sciences; he would find them heavily involved in graduate education in many basic medical and biological sciences; and he would find them increasingly concerned with programs of continuing lifetime education for our medical practitioners.

With these observations, it would be clear to Dr. Flexner that the battle to provide a scientific basis for medicine had been won, and that the struggle to improve and upgrade academically our medical education system, for which his report sounded the clarion call, had been fought to a successful conclusion.

And Dr. Flexner would observe that the achievement of these victories has been due in no small measure to the continuing generous support Congress has given to efforts to advance medical science and the health of our people.

Mr. O'Connor alleges that increased funds have resulted in "scientific log-rolling." He says, "I would describe it as scientific logrolling perpetuated in the field of medicine by a relatively small group of researchers and others who advise the Government on its role in the health sciences and who also pass on support for each others investigations."

This serious accusation is not true.

Since the inception of the grant program the PHS has sought the advice and counsel of the Nation's leading scientists and clinical investigators in the evaluation of applications and in the development of policy and programs. The different individuals who have served in this manner number literally in the thousands. Men are chosen for these diverse tasks because of their established reputations for eminence in their field for scientific productivity, for critical judgment, and for personal integrity. At the present moment there are almost 200 formally established advisory groups and on an ad hoc basis the PHS utilizes almost 100 more. Unfortunately the group of individuals meeting those criteria that must be drawn from is indeed small, but that is an inherent limitation that will continue in fields of specialized scientific activity. This process is not subject to the abuse charged by Mr. O'Connor.

This system of using non-Federal consultants for evaluation and advice employed by the PHS is also the system used by the National Science Foundation and other Federal agencies, and is widely admired throughout the world. The recent report of the Council on Medical Education and Hospitals of the American Medical Association, pages 35 and 36, states:

"Grants from NIH are awarded only after careful review of each application by study sections composed of leading scientists, many of them members of a medical school faculty. Following this, the applications are approved by an advisory council consisting of outstanding citizens. This system has been applauded by educators, scientists, Congressmen, and others. The system has been copied, with modifications, by other agencies including many of the voluntary health agencies."

Mr. O'Connor expresses the view that laymen are not now adequately represented in the advisory groups upon which the Public Health Service depends in the conduct of its programs.

Each of the national advisory councils has lay representatives in accordance with the provisions of law establishing such councils. The PHS has always sought the advice and views of leading citizens on matters relating to health policy and the development of our programs and has gained much from the breadth of their point of view and their lack of commitment to any particular field of endeavor. The fact that most of the advisory councils must reach

judgments in respect to research and scientific proposals has presented problems in respect to the more extensive use of laymen in such specialized areas. The Public Health Service has long recognized the need for an advisory body that could consider policy issues and national health problems unencumbered by the dual responsibility of reviewing specific applications for research support. At the present moment it is considering the reconstituting of the National Advisory Health Council. This Council has the function of providing advice to the Surgeon General with respect to matters broadly concerned with the advancement of the Nation's health. Up until very recently it has also had a substantial role in the review and evaluation of research proposals relating to the program of the Division of General Medical Sciences of the National Institutes of Health. With the elevation of this Division to Institute status and the creation of its own advisory council, as provided for in legislation enacted by the last Congress, it is now possible to utilize the National Advisory Health Council in the broad way in which the original legislation creating it intended. Serious consideration is being given to providing more adequate representation to leading citizens outside the professional health fields precisely because the function of this Council is now changed. The view of such individuals will be of great assistance in the development of policies and programs required to meet more adequately the Nation's health needs.

Mr. O'Connor charges that the "plethora" of funds actually constitute a prospective threat to the quality of scientific work being done; that is, it is forcing scientists to spend rather than to think and turning them into administrators, and that scientific effort is threatened by the present level of support for medical research.

What is happening in the medical research world is substantially different from the view expressed by Mr. O'Connor. The biomedical sciences has emerged into an era, in large part brought about by the past 15 years of expanding support for scientific work in this field, that presents a totally new and different set of challenges to the scientific community.

In the first place, the world has witnessed increasing sophistication in the technology, the scientific capability, and the diversity of skills that we can bring to bear upon scientific problems in the health field. Increasingly, effective research effort today involves complex instrumentation, a diversity of supporting technical staffs, large-scale specialized clinical and laboratory facilities. The pursuit of the solution of many major health problems must engage the co-ordinated efforts of investigators representing many disciplines working in a joint framework upon various aspects of such problems.

Secondly, it is important to understand that the frontier of knowledge relating to disease, life processes, and the maintenance of health has been pushed to the point now where the horizon of the unknown presents the most complex and difficult challenges encountered in the whole history of the medical sciences. The further extension of this frontier in terms of the gaining of new knowledge calls for greater and greater effort. Unfortunately, the price of new knowledge today in any scientific field simply because of the increasing complexity and difficulty of the problems to be solved, must ever rise higher and higher. This fact is not a threat to excellence. On the contrary, the very challenge that these difficult problems present is bringing into being a better trained, a more dedicated, and a vastly more capable group of scientists than has been the generality of the past.

SUMMARY STATEMENTS AND TABLES

(Following are the statements and tables the chairman stated earlier would be placed in the record at the end of this section of the hearings with NIH.)

DESCRIPTION OF EACH NIH GRANT PROGRAM

REGULAR RESEARCH GRANTS

1. Purpose of the program

To provide grant support of research in health, medicine, and allied fields with the major objectives (1) of expanding medical and biological research activities in universities, hospitals, laboratories, and other public or private institutions

and (2) of stimulating new investigations in fields needing exploration. The grant ranges from support of smaller, discrete, and circumscribed projects, which are defined as project grants, to support of broad programs which integrate the research interests of several investigators, and which are called program project grants.

2. Funds

1959 obligations_____	\$139, 629, 000
1960 obligations_____	185, 474, 000
1961 obligations_____	240, 607, 000
1962 obligations_____	305, 527, 000
1963 estimates_____	374, 668, 000
1964 estimates_____	454, 981, 000

3. Present stage of development

The modest cancer grants program of 1938-45 of less than \$100,000 annually changed in 1946 to a health, medicine, and related sciences program of \$780,000. Steady annual increases since 1946 have produced the 1963 program of almost \$400 million. This \$400 million will support more than 15,000 research projects conducted in almost 1,500 institutions throughout this country and abroad, and covering the full range of biological and related research. While the program continues in major part to support the ideas of investigators in the grantee institutions, a significant part of the grants provide support of programs reflecting initiative of NIH staff, such as cancer chemotherapy, psychopharmacology, and other collaborative programs.

4. Plans for the future

The NIH believes that medical research should continue to expand as long as this country is faced with major crippling and killing diseases and conditions. Further, it believes that a number of factors contribute together to provide full assurance that substantial expansion can be effected. These factors include (1) a sharp expansion in the population base from which new M.D.'s and Ph. D.'s will be drawn, (2) a steadily rising college enrollment, (3) a significant percentage increase in graduate enrollment, and (4) improving educational opportunities for the more talented students, including both new medical schools and strengthened graduate and professional schools.

CLINICAL RESEARCH CENTERS¹

1. Purpose of program

To provide grants to non-Federal research institutions for establishment of biomedical research centers of resources. These centers make possible the performance of meritorious and complex clinical investigation in the preclinical, clinical, and health-related sciences. They provide the opportunity for precise observations and controls which are essential to studies with patients. These centers administratively may be viewed as (a) categorical and (b) general. The categorical centers are supported by the appropriate Institute and are concerned primarily with a specific category or type of disease, such as heart disease or cancer, toward which the work of the particular Institute is oriented. In the General Clinical Research Centers program, which is supported by the Division of Research Facilities and Resources, the research activity is not focused primarily on a single Institute-related category of disease, but rather on categories of disease and on numerous areas of preclinical and clinical science. All centers consist of discrete facilities with specialized bed arrangements, core laboratories, and trained personnel. They use a multidisciplinary approach wherein investigators with varied interests and techniques share the center's facilities. The centers are highly conducive to the advancement of knowledge regarding human health and disease.

¹ Includes physical resources portions of program projects.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE,
AND NATIONAL INSTITUTES OF HEALTH

2. *Funding of clinical research centers program (research center grants and physical resource component of program project grants)*

[In thousands]

	Obligations, 1960	Obligations, 1961	Obligations, 1962	Estimate, 1963	Estimate, 1964
Division of General Medical Sciences-----	¹ \$2,993	¹ \$8,000	\$22,123	\$33,500	\$27,900
Cancer-----		4,199	805	4,833	4,900
Mental-----		509	700	2,000	1,750
Heart-----		3,962	1,782	3,000	1,600
Dental-----				350	350
Arthritis-----			481	1,750	1,250
Allergy-----			500	1,000	1,000
Neurology-----		537	577	1,500	1,200
Total-----	2,993	17,207	26,968	47,933	39,950

¹ Includes obligations incurred against funds appropriated to the categorical Institutes totaling \$3,000,000.

3. *Present state of development*

The earlier of the center's program, general clinical research centers, is now well underway with 56 grants having been made to 50 institutions as of December 31, 1962. It is anticipated that awards will have been made to 70-80 centers by the end of 1963. Important scientific accomplishments have already been noted.

Forty-five categorical center grants were awarded in fiscal year 1962. The funds available in 1963 will support awards for 60-80 centers. As with the general clinical research centers program, the categorical programs have made important progress.

4. *Plans for the future*

The 1964 President's budget will provide full continuation and supplemental support to the centers receiving awards in 1963 and provide support for approximately six additional general centers.

SPECIAL RESOURCE CENTERS

1. *Purpose of the program*

To provide grants to non-Federal research institutions for support of specialized facilities that provide the basic tools of research and specialized services necessary for the support of institutional research programs. Such tools may consist of computers, highly trained technical staff, costly and complex instrumentation, or other aids to a large research operation.

2. *Funds*

1962 obligations-----	\$4,329,000
1963 estimate-----	6,000,000
1964 estimate-----	6,000,000

3. *Present state of development*

In 1962, the initial year for this program, 14 grants were awarded for a total of \$4,329,000. Nine additional awards have been for 1963 support as of December 31, 1962.

4. *Plans for the future*

The 1964 President's budget will support this program at the 1963 level.

PRIMATE RESEARCH CENTERS PROGRAM

1. *Purpose of program*

To provide funds for the construction and basic operation of special research facilities or centers devoted to the advancement of all areas of knowledge on the biological characteristics of species structurally and physiologically similar to man throughout the entire lifespan of the subhuman primate. The objective is to acquire basic scientific information which will ultimately be useful in the pre-

vention and treatment of human disease. Research facilities provided by this program are available to visiting scientists from all areas of this country and abroad.

2. Funds

1960 obligations-----	\$1, 917, 000
1961 obligations-----	7, 000, 000
1962 obligations-----	9, 495, 000
1963 estimate-----	5, 120, 000
1964 estimate-----	5, 700, 000

3. Present stage of development

A total of seven primate center awards have been made. Each of these awards has provided two grants, one for all construction costs, including acquisition of land, and one for either total or base operating costs for 7 years. The first award was made in 1960 to the Medical Research Foundation of Oregon. This center is now in operation.

Three awards were made in fiscal year 1961, one to the University of Wisconsin, one to the University of Washington, and one to Emory University in Georgia. The final construction plans for the Washington Center are now in the drafting stage, and construction is expected to begin early in 1963. Construction of the Wisconsin Center was begun in October 1962, and construction at Emory University is scheduled to begin late in 1963.

Three awards were made during fiscal year 1962, one to Harvard University, one to Tulane University, and one to the University of California. The latter award will operate as a national conditioning center. The construction of these three centers is scheduled to begin late in 1963.

According to present schedules, all seven of these primate research centers will be in operation by the end of 1964.

4. Plans for the future

The requested funds in the 1964 President's budget will allow for the support, maintenance, and some supplementation of the seven centers mentioned above.

GENERAL RESEARCH SUPPORT GRANTS

1. Purpose of program

To provide funds for the general support of the medical research and research training programs of institutions under conditions enabling the recipients to meet needs which could not be effectively met by other forms of support. The grants can be utilized for such purposes as capitalizing on emerging research opportunities, exploring new and unorthodox ideas, or stimulating and developing an overall research or research training program. The broad type of support made possible through these grants can enable an institution to achieve a better balance in their total research and training programs, and permit the recipient institutions to strengthen the administration of these programs under conditions and in directions of their own choice.

2. Funds

The amount available for distribution to this program constitutes "such uniform percentage, not to exceed 15 per centum, as the Surgeon General may determine, of the amounts provided for grants for research projects for any fiscal year through the appropriations for the National Institutes of Health * * *" (Public Law 86-798). In 1962, approximately 6 percent of appropriated funds for regular research projects was devoted to general research support grants. Approximately 7 percent of the 1963 estimated obligations, and 6 percent of the 1964 requested funds will be directed to this program.

1962 obligations-----	\$20, 000, 000
1963 estimate-----	30, 000, 000
1964 estimate-----	30, 000, 000

3. Present state of development

General research support grants were awarded in 1962 to 153 professionally accredited schools of dentistry, medicine, osteopathy, and public health. In 1963, the program is being extended to other accredited professional schools and certain nonprofit research institutions deemed eligible by the National Advisory Health Council. These include schools of nursing, pharmacy and veterinary

medicine, and research institutions, centers, hospitals and laboratories heavily engaged in research.

The formula for the distribution of these grants provides funds proportionate to the total volume of research conducted by these institutions, with particular weight given to the institutes budgeted research funds from non-Federal sources.

4. *Plans for the future*

The 1964 President's budget maintains this program at the 1963 level.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

1. *Purpose of program*

Research grants are awarded in this program to American universities to enable these universities to establish centers within both their own organizations and in affiliate centers within foreign institutions to broaden collaborative research and research training in the biomedical fields.

2. *Funds*

In 1961, this program was administered by the National Institute of Allergy and Infectious Diseases and supported by six of the Institutes plus the Division of General Medical Sciences. This same situation existed in 1962 except for the absorption by Allergy of the support of Heart and Arthritis Institutes. In 1963, the program is being administered by the Office of International Research, OIR, part of the Office of the Director, NIH. In 1964, OIR will be incorporated into the G.R. & S. appropriation.

1961 obligations-----	\$1, 937, 000
1962 obligations-----	2, 093, 000
1963 estimate-----	3, 692, 000
1964 estimate-----	3, 000, 000

3. *Present stage of development*

There are five centers currently being supported. The institutions involved and their respective programs are as follows:

A. University of California Schools of Medicine and Public Health, and the Hooper Foundation in collaboration with the Institute for Medical Research, Kuala Lumpur, Malaya.

The research program is initially centered on arthropodborne virus diseases, mycology, endocrinology, parasitology, and entomology with training emphasis in the fields of endocrinology-metabolism, biochemistry-immunology, microbiology-virology, geographic pathology, and medical ecology.

B. Johns Hopkins University School of Hygiene and Public Health and Department of Medicine in collaboration with the School of Tropical Medicine, Calcutta.

The research program has primary interests directed to the fields of pathology and general medicine, with emphasis on hematologic, infectious neoplastic, and nutritional diseases.

C. University of Maryland School of Medicine in collaboration with the Institute of Hygiene, Lahore, West Pakistan, and other cooperating institutions in the area.

The general research program has emphasis centered initially on fevers of unknown origin, gastrointestinal infections, parasitology, pulmonary disorders, nutrition, pediatrics, preventive medicine, and epidemiology.

D. Tulane University School of Medicine in collaboration with the Universidad del Valle, Cali, Colombia.

E. Louisiana State University (New Orleans). The faculty of the school of medicine in pursuing studies in Central America.

The overall research approach will include studies in virology, bacteriology, parasitology, mycology, metabolism, biometry, and pathology of chronic diseases, such as cancer and vascular diseases.

4. *Plans for the future*

The 1964 President's budget provides \$3 million for the continuation of this program.

RESEARCH CAREER AWARDS

1. Purpose of the program

The purpose of this program is to provide increased numbers of stable career opportunities for scientists of superior potential and capability in the sciences related to health. The program includes young investigators who desire experience and further training in a productive research environment; scientists need experience to qualify for senior positions; and experienced investigators who are continuing to develop in productive careers of independent teaching and research.

2. Funds

The research career award program was initiated in 1962 by merging, modifying, and absorbing the career research professorship components of the special fellowships and the senior fellowship programs. The growth of the program is shown in the figures below :

1962 obligations-----	\$10, 012, 000
1963 estimate-----	18, 417, 000
1964 estimate-----	19, 409, 000

3. Present stage of development

Approximately 1,077 awards will be made in 1963 by each of the Institutes and the Division of General Medical Sciences. This is almost twice the number awarded in 1962.

4. Plans for the future

The increased funds requested in the 1964 President's budget will be used to expand this program in the National Institute of Mental Health, allowing this Institute to make approximately 53 additional awards.

SCIENTIFIC EVALUATION AND PLANNING GRANTS (CHAIRMAN'S GRANTS)

1. Purpose of the program

To provide funds for the assistance of the National Advisory Councils through the technical and scientific review of grant applications, and through the support of meetings used for the exchange of scientific views.

2. Funds

1961 obligations-----	\$1, 734, 000
1962 obligations-----	1, 244, 000
1963 estimate-----	1, 269, 000
1964 estimate-----	1, 350, 000

3. Present stage of development

Research grant applications are reviewed prior to submission to the advisory councils by the appropriate "study section." Each of these sections has scientific competency in a particular field or research discipline, and each is comprised of outstanding civilian authorities in the relevant specialties. In the training area, individual applications are reviewed by groups called committees. Both the study sections and the committees are supported by chairman's grants.

In addition to financing these review activities, chairman's grants support an extensive group of ad hoc panels, symposia, conferences, and other types of meetings used for the exchange of professional views.

REGULAR RESEARCH FELLOWSHIPS

1. Purpose of program

The purpose of the program is to support the training of qualified scholars for research and academic careers in the basic and clinical sciences in health and health-related fields and thereby to increase the number of trained research investigators and teachers in these fields.

There are three major categories of regular research fellowships : Predoctoral, postdoctoral, and special.

Predoctoral fellowships are to assist individuals who have a bachelor's degree or equivalent in such training in the aforementioned fields as leads to a master's or doctoral degree. Postdoctoral fellowships are to support additional training for an individual who already has earned Ph. D., M.D., D.D.S., D.V.M., or

equivalent degree. Special fellowships are to support groups of fellows who fit into one of the following: (1) Those who have had at least 3 years of relevant research and/or professional experience after receipt of the doctoral degree; (2) those who have completed residency training requirements in a clinical specialty or its equivalent; and (3) those who need special training not met by other fellowship programs although they do not have a doctoral or equivalent degree.

2. Funds: Regular research fellowships

	Predoctoral	Postdoctoral	Special	Total
1959 obligations.....	\$3,180,000	\$3,728,000	\$901,000	\$7,809,000
1960 obligations.....	4,783,000	5,332,000	1,342,000	11,457,000
1961 obligations.....	5,200,000	6,857,000	2,188,000	14,245,000
1962 obligations.....	4,706,000	8,597,000	2,509,000	15,812,000
1963 estimate.....	7,481,000	10,076,000	3,748,000	21,305,000
1964 estimate.....	9,417,000	11,380,000	4,380,000	25,177,000

3. Present stage of development

Approximately 1,441 predoctoral fellows will be supported in 1963 for the general, mental, and dental programs, an increase of 35 over the 1962 level. Approximately 1,417 postdoctoral fellows will be supported in 1963 by all institutes and the general program. This is an increase of 188 over the 1962 level. Approximately 402 special fellows will be supported in 1963 by all programs except neurology. This is an increase of 129 over the 1962 level.

4. Plans for the future

The 1964 President's budget will provide additional support to approximately 349 predoctoral, 188 postdoctoral, and 71 special fellows.

FOREIGN FELLOWSHIPS

1. Purpose of the program

This program provides awards to promising foreign scientists to support their training in U.S. laboratories. Although it undoubtedly contributes to the improvement of foreign research capabilities, the objectives of the program are essentially domestic. One purpose, for instance, is to enrich the postgraduate biomedical training in this country by enabling foreign investigators to share their ideas and background with American colleagues. Another is to encourage foreign scientists to participate in research bearing upon American health problems. As this research is often continued and extended by the fellow upon return to his home country, additional opportunities are created for future collaborative efforts in research endeavors of importance to the United States.

2. Funds

1959 obligations.....	\$345,000
1960 obligations.....	400,000
1961 obligations.....	700,000
1962 obligations.....	700,000
1963 estimate.....	1,200,000
1964 estimate.....	1,200,000

3. Present stage of development

This program was established in Western Europe in fiscal year 1958 with 12 countries participating. Plans were made at that time for an orderly increase in the number of participating countries based on research potential and likelihood that returning fellows would use training in the United States. The increase in the number of participating countries has progressed according to schedule as follows: 1959, 30; 1960, 36; 1961, 40; 1962, 41; and in 1963 an esti-

mated 43. There will be 155 fellows supported in 1963 as contrasted with 92 in 1962.

4. *Plans for the future*

The 1964 President's budget maintains this program at the 1963 level.

TRAINING GRANTS

1. *Purpose of program*

To provide grant support of training in specified aspects of health, medicine, and allied fields with the major objectives of (a) insuring an adequate supply of competent research manpower, (b) alleviating critical shortages of professional personnel in certain areas affecting research teaching and service, and (c) facilitating within the student bodies of health-related professional schools the development of knowledge about special areas of disease that have particular significance. The training grant fulfills a dual function. Its funds underwrite certain expenses related to the specific training mission, including the provision of stipends to individuals selected for that training except in (c) above. It also serves to create and maintain an atmosphere essential to the training by providing a focal point for the specific discipline or disease within the training institutions.

2. *Funds*

1959 obligations-----	\$49, 812, 000
1960 obligations-----	74, 673, 000
1961 obligations-----	109, 928, 000
1962 obligations-----	114, 585, 000
1963 estimate-----	145, 297, 000
1964 estimate-----	172, 602, 000

3. *Present stage of development*

The National Institute of General Medical Sciences program is oriented toward disciplines which cannot be categorized according to specified diseases. The categorical programs are directed toward the prevention and cure of specific categories of diseases for which the Institutes other than NIGMS have assigned responsibilities. NIGMS support is provided through awards of fellowships and training grants which support the training of both predoctoral and postdoctoral trainees in the basic sciences. The categorical institutes utilize the same forms of support but the primary emphasis of their training programs is the predoctoral training of Ph. D.'s, M.D.'s, D.D.S.'s, D.V.M.'s, etc., to provide the blend of specialized research and clinical training that is essential for careers of research investigations and teaching in the health sciences.

4. *Plans for the future*

The recruitment and training of scientists in the fundamental, biological, and medical sciences are required as part of the general effort to expand the scientific competence of the Nation. Indeed, the key to the biological research anticipated in the future lies in the provision of trained manpower adequate in both quantity and quality. Accordingly, the factors cited in support of an expanded research grant program substantiate the necessity for increased training activities. In addition, increased needs for teachers and for personnel for medical services generate supplemental needs for training in specialized fields. The NIH training grant program is an integral and indispensable part of a total national effort to fulfill these needs. In terms of institutional objectives, the training grant is a uniquely valuable means of integrating efforts to deal with specific diseases or discipline problems. Although the characteristics of the program will change in response to changing requirements, such as the emerging needs to recruit scientists at the undergraduate level and to intensify programs for the training of technicians, the basic objectives of the programs will remain constant, and the attainment of these objectives will require an orderly annual expansion of expenditures.

HISTORY OF THE 1964 NIH BUDGET

SUMMARY

Chronological development of overall budget for 1964

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate to Department of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$690,450	-\$65,733	\$624,717	-\$69,136	\$555,581	-\$14,350	\$541,231
Fellowships.....	57,085	+1,099	58,184	-9,121	49,063	-3,277	45,786
Training.....	197,724	-15,590	182,134	-5,783	176,351	-3,749	172,602
State control programs.....	15,000	-4,050	10,950	0	10,950	0	10,950
Total grants.....	960,259	-84,274	875,985	-84,040	791,945	-21,376	770,569
Direct operations:							
Research.....	78,339	-3,593	74,746	-2,502	72,244	-1,106	71,138
Collaborative studies.....	67,146	-1,852	65,294	-6,493	58,801	-741	58,060
International research.....	854	+219	1,073	0	1,073	0	1,073
Biologics standards.....	4,767	+71	4,838	0	4,838	-51	4,787
Training activities.....	1,709	-82	1,627	0	1,627	-162	1,465
Professional and technical assistance.....	9,982	-5,446	4,536	-390	4,146	-148	3,998
Review and approval.....	17,274	-357	16,917	-1,398	15,519	-348	15,171
Program direction.....	4,223	+586	4,809	-509	4,300	-107	4,193
Total direct operations.....	184,294	-10,454	173,840	-11,292	162,548	-2,663	159,885
Total obligations.....	1,144,553	-94,728	1,049,825	-95,332	954,493	-24,039	930,454

EXPLANATION OF CHANGE—OVERALL NATIONAL INSTITUTES OF HEALTH

DHEW action

The major change between the preliminary estimate to the DHEW and the subsequent estimates to the BOB was in research grants. The NIH proposed support for payment of all continuations, supplementals, and new grants. The Department approved payment of all noncompeting continuations, but maintained support of competing continuations, supplementals, and new grants at the 1963 dollar level with the exception of the mental health area where an increase was approved for new grants to reflect the recommendations stemming from the Joint Commission on Mental Illness and Health and the President's Panel on Mental Retardation. The Department reduced general research support grants from \$40 to \$35 million; general clinical research centers from \$45 to \$38.5 million; categorical centers from \$20.1 to \$14.5 million; special resource centers from \$10 to \$6 million; and primate centers from \$6.5 to \$6 million. The DHEW allowance, however, provided increases over the 1963 dollar level of 15 percent for general clinical research centers, 17 percent for general research support grants, and 17 percent for primate centers, respectively. Special resource centers are included at the 1963 level of \$6 million.

Reductions were made in training grants and fellowships in the amount of \$14.9 million. However, the total DHEW allowance included increases of \$39.2 million over the 1963 operating level, of which \$19.2 million was proposed for mental health and mental retardation activities.

The changes in the direct operations programs, with the exception of mental health, affected expansion of the cancer virus and research contract programs; heart cardiovascular studies and clinical surgery research; arthritis nutrition research; neurology perinatal research; expansion in direct research laboratories; and in epidemiological and biometrical studies. Decreases in the review and approval activity reflect reductions effected in the research grants area.

Bureau of the Budget action

The NIH had proposed support for payment of additional indirect costs up to 20 percent for all grants approved for support in 1964. The DHEW approved this request. In addition, the Bureau of the Budget proposed payment of indirect costs at a maximum of 25 percent on grants approved on or after January 1, 1964. Support for general clinical research centers and categorical clinical research centers was reduced from \$38.5 to \$27.9 million and \$14.5 to \$14.1 million, respectively. Though they represented decreases over the 1963 level, these amounts proposed for 1964 are sufficient to provide for the full continuation and supplemental support for both the general and categorical programs, and for the support of approximately six new general clinical centers. General research support grants were reduced from \$35 million to the 1963 dollar level of \$30 million. The BOB reduced the request for fellowships by 7 percent and training grants by 2 percent; the approved amounts, however, provided increases over the 1963 dollar level of 6 percent for fellowships and 11 percent for training grants, respectively.

Changes in intramural research affected mental health brain and behavior studies; mental health professional and technical assistance research utilization program; and the arthritis international nutrition program.

Mental health expansion and mental retardation

The proposed amendment was approved at \$31.4 million, a reduction of \$1.2 million from the requested amount. The research grants portion was reduced from \$16.6 to \$15.6 million and training grants was reduced from \$11.5 to \$11.3 million.

GENERAL RESEARCH AND SERVICES

Development of 1964 budget estimates for general research and services

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate to Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$152,729	—\$10,590	\$142,139	—\$23,641	\$118,498	—\$11,969	\$106,529
Fellowships.....	18,884	+2,500	21,384	—4,737	16,647	—1,370	15,277
Training.....	50,134	—10,000	40,134	—1,716	38,418	—1,162	37,256
Total grants.....	221,747	—18,090	203,657	—30,094	173,563	—14,501	159,062
Direct operations:							
Collaborative studies.....	0	+2,000	2,000	—2,000	0	0	0
International research.....	854	+219	1,073	0	1,073	0	1,073
Training activities.....	0	+300	300	0	300	—150	150
Review and approval.....	3,374	+160	3,534	—343	3,191	—60	3,131
Program direction.....	820	+517	1,337	—98	1,239	+19	1,258
Total direct operations.....	5,048	+3,196	8,244	—2,441	5,803	—191	5,612
Total obligations.....	226,795	—14,894	¹ 211,901	—32,535	179,366	—14,692	164,674

¹ Reduction of \$500,000 for primate centers is reflected in the heart appropriation.

BIOLOGICS STANDARDS

Development of 1964 budget estimates for biologics standards

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate to Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Direct operations:							
Biologics standards.....	\$4,767	+\$71	\$4,838	0	\$4,838	-51	\$4,787
Total direct operations.....	4,767	+71	4,838	0	4,838	-51	4,787
Total obligations.....	4,767	+71	4,838	0	4,838	-51	4,787

CANCER

Development of 1964 budget estimates for National Cancer Institute

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate to Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$73,073	-\$3,184	\$69,889	-\$4,859	\$65,030	+\$223	\$65,253
Fellowships.....	6,180	+20	6,200	-928	5,272	-84	5,188
Training.....	15,095	-1,895	13,200	-448	12,752	-232	12,520
Total grants.....	94,348	-5,059	89,289	-6,235	83,054	-93	82,961
Direct operations:							
Research.....	19,409	-959	18,450	-1,025	17,425	-184	17,241
Collaborative studies.....	46,386	-2,062	44,324	-1,936	42,388	-268	42,120
Review and approval.....	1,998	-55	1,943	+52	1,995	-26	1,969
Program direction.....	937	+56	993	-149	844	-21	823
Total direct operations.....	68,730	-3,020	65,710	-3,058	62,652	-499	62,153
Total obligations.....	163,078	-8,079	154,999	-9,293	145,706	-592	145,114

MENTAL HEALTH

Development of 1964 budget estimates for mental health activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1964 President's budget
Grants:							
Research.....	\$103,350	-\$9,826	\$93,524	-\$11,669	\$81,855	-\$1,100	\$80,755
Fellowships.....	9,280	+40	9,300	+4	9,304	-770	8,534
Training.....	65,000	+1,800	66,800	-6	66,794	-746	66,048
State control programs.....	15,000	-4,050	10,950	0	10,950	0	10,950
Total grants.....	192,610	-12,036	180,574	-11,671	168,903	-2,616	166,287
Direct operations:							
Research.....	12,358	-1,607	10,751	+103	10,854	-246	10,608
Collaborative studies.....	4,149	+304	4,453	-2	4,451	-88	4,363
Training activities.....	1,008	-7	1,001	0	1,001	0	1,001
Professional and technical assistance.....	6,987	-2,451	4,536	-390	4,146	-148	3,998
Review and approval.....	4,532	-438	4,094	-798	3,296	-62	3,234
Program direction.....	743	-91	652	-26	626	-21	605
Total direct operations.....	29,777	-4,290	25,487	-1,113	24,374	-565	23,809
Total obligations.....	222,387	-16,326	206,061	-12,784	193,277	-3,181	190,096

HEART

Development of 1964 budget estimates for National Heart Institute

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1964 President's budget
Grants:							
Research.....	\$115,547	-\$7,295	\$108,252	-\$9,896	\$98,356	-\$1,173	\$97,183
Fellowships.....	7,800	+200	8,000	-1,347	6,653	-254	6,399
Training.....	19,000	-2,100	16,900	-755	16,145	-966	15,179
Total grants.....	142,347	-9,195	133,152	-11,998	121,154	-2,393	118,761
Direct operations:							
Research.....	11,319	-208	11,111	-306	10,805	-197	10,608
Collaborative studies.....	2,010	-184	1,826	-380	1,446	-20	1,426
Training activities.....	600	-350	250	0	250	0	250
Review and approval.....	2,400	-52	2,348	-115	2,233	-50	2,183
Program direction.....	484	+14	498	-86	412	-16	396
Total direct operations.....	16,813	-780	16,033	-887	15,146	-283	14,863
Total obligations.....	159,160	-9,975	149,185	-12,885	136,300	-2,676	133,624

DENTAL

Development of 1964 budget estimates for National Institute of Dental Research

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate to Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$9,769	+\$1,128	\$10,897	-\$1,089	\$9,808	+\$25	\$9,833
Fellowships.....	1,500	+100	1,600	-243	1,357	-100	1,257
Training.....	4,515	+1,985	6,500	-1,445	5,055	-250	4,805
Total grants.....	15,784	+3,213	18,997	-2,777	16,220	-325	15,895
Direct operations:							
Research.....	3,777	-227	3,550	-280	3,270	-70	3,200
Review and approval.....	505	+62	567	-32	535	-6	529
Program direction.....	183	+17	200	-13	187	-2	185
Total direct operations.....	4,465	-148	4,317	-325	3,992	-78	3,914
Total obligations.....	20,249	+3,065	23,314	-3,102	20,212	-403	19,809

ARTHRITIS AND METABOLIC DISEASE

Development of 1964 budget estimates for arthritis and metabolic disease activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate of Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$110,295	-\$21,096	\$89,199	-\$6,417	\$82,782	-\$269	\$82,513
Fellowships.....	5,000	0	5,000	-704	4,296	-277	4,019
Training.....	17,900	-2,900	15,000	-580	14,420	0	14,420
Total grants.....	133,195	-23,996	109,199	-7,701	101,498	-546	100,952
Direct operations:							
Research.....	12,196	-123	12,073	-644	11,429	-122	11,307
Collaborative studies.....	1,188	+33	1,221	-220	1,001	-288	713
Review and approval.....	1,800	-70	1,730	-195	1,535	-66	1,469
Program direction.....	355	+1	356	-60	296	-20	276
Total direct operations.....	15,539	-159	15,380	-1,119	14,261	-496	13,765
Total obligations.....	148,734	-24,155	124,579	-8,820	115,759	-1,042	114,717

ALLERGY AND INFECTIOUS DISEASE

Development of 1964 budget estimates for allergy and infectious disease activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate to Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$60,441	-\$12,857	\$47,584	-\$6,975	\$40,609	+\$19	\$40,628
Fellowships.....	5,981	-1,981	4,000	-720	3,280	-222	3,058
Training.....	9,980	-1,580	8,400	-315	8,085	-93	7,992
Total grants.....	76,402	-16,418	59,984	-8,010	51,974	-296	51,678
Direct operations:							
Research.....	11,684	-178	11,506	-320	11,186	-205	10,981
Collaborative studies.....	8,715	-2,000	6,715	-1,424	5,291	-7	5,284
Review and approval.....	1,021	-1	1,020	-11	1,009	-17	992
Program direction.....	284	+60	344	-39	305	-14	291
Total direct operations.....	21,704	-2,119	19,585	-1,794	17,791	-243	17,548
Total obligations.....	98,106	-18,537	79,569	-9,804	69,765	-539	69,226

NEUROLOGY AND BLINDNESS

Development of 1964 budget estimates for neurology and blindness activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Prelimi- nary estimate of Depart- ment of Health, Educa- tion, and Welfare	Change	Depart- ment of Health, Educa- tion, and Welfare to Bureau of the Budget	Change	1964 Presi- dent's budget
Grants:							
Research.....	\$65,246	-\$2,013	\$63,233	-\$4,590	\$58,643	-\$106	\$58,537
Fellowships.....	2,480	+220	2,700	-446	2,254	-200	2,054
Training.....	16,100	-900	15,200	-518	14,682	-300	14,382
Total grants.....	83,826	-2,693	81,133	-5,554	75,579	-606	74,973
Direct operations:							
Research.....	7,596	-291	7,305	-30	7,275	-82	7,193
Collaborative studies.....	4,698	+57	4,755	-531	4,224	-70	4,154
Training activities.....	101	-25	76	0	76	-12	64
Professional and technical assistance.....	2,995	-2,995	0	0	0	0	0
Review and approval.....	1,644	+37	1,681	+44	1,725	-61	1,664
Program direction.....	417	+12	429	-38	391	-32	359
Total direct operations.....	17,451	-3,205	14,246	-555	13,691	-257	13,434
Total obligations.....	101,277	-5,898	95,379	-6,109	89,270	-863	88,407

PROFESSIONAL JUDGMENT BUDGETS

SUMMARY OF PROFESSIONAL JUDGMENT BUDGETS SUBMITTED BY NIH INSTITUTE DIRECTORS

The Directors of the several Institutes and Chiefs of the program Divisions of the National Institutes of Health have submitted estimates for 1964 which reflect in their best professional judgment the total funds which could be used for their individual programs.

These estimates have not been influenced by the Office of the Director, National Institutes of Health, the Office of the Surgeon General, or the Office of the Secretary through guidelines or review such as normally occur in the budgetary process. They do not, therefore, represent in the aggregate an NIH budgetary proposal. Consideration has not been given to those factors which normally influence budget proposals, such as—

(1) The consistency of the proposals of individual Institutes with existing congressional directives and legislation.

(2) The appropriateness of relative emphasis among programs as for example between research grants and training grants.

(3) The adequacy of manpower, space, and other resources when the total budgets of all Institutes are added up.

(4) The effect of combined Institutes' proposals upon educational institutions.

(5) The sum total of all proposals in relation to fiscal feasibility and other broad policy considerations.

(6) The effect of projected program increases upon the central (NIH) management requirements.

GENERAL RESEARCH AND SERVICES

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research (ICMRT).....	\$3, 000	\$4, 000	\$1, 000
Fellowships (international postdoctoral).....	1, 200	1, 200	0
Total, grants and related contracts.....	4, 200	5, 200	1, 000
Direct operations:			
International research.....	1, 073	1, 138	65
Training activities (IRAP).....	150	300	150
Total, direct operations.....	1, 223	1, 438	215
Total estimate.....	5, 423	6, 638	1, 215

1. Grants, increase of \$1 million

A. Research grants, increase of \$1 million.—From the international centers program established in 1960 there are now emerging vigorous interdisciplinary programs of research and research training in each of the five ICMRT's at their U.S. and overseas facilities. Experience in the program indicates that it is now playing an increasingly important role in enlarging U.S. resources of scientific manpower and facilities essential for the conduct of international research which is relevant to the advancement of the health sciences in the United States. The ICMRT concept provides for the first time an unusual opportunity to attack and solve medical problems of worldwide significance which lie outside the scope of any single discipline through the skillful cooperation of biologists, physicians, behavioral and social scientists.

Achievements to date reflect the prudent selection and planning of those developmental programs which possessed greatest potential for creative research and the evolution of superior research training. Grant support for each ICMRT

has been limited to an expenditure of \$500,000 or less annually. This level of funding has been sufficient for basic maintenance of the centers during program development. Currently expanding activities, newly initiated research projects, rapidly enlarging professional staffs with associated training programs and increases in necessary travel contribute to the growing need for increased base support. An increase of \$500,000 will provide for these additional expenditures in each international center during fiscal year 1964.

The continued success of the ICMRT program would indicate that the establishment of an additional center based in Africa will be considered in fiscal year 1964. Several U.S. universities have demonstrated their serious interest in sponsoring such a program; the institution to undertake the development of a new ICMRT will be selected after appropriate scientific and administrative review by the Advisory Committee on International Centers for Medical Research and Training. It is estimated that an additional \$500,000 would finance a new center through its initial year of operation.

B. Fellowship (International Postdoctoral).—No increase.

2. Direct operations, increase of \$215,000

A. International research, increase of \$65,000.—An additional \$65,000 and six positions are required in relation to the existing program responsibilities in OIR.

International research associate program, two positions: Two positions will be necessary to administer the expanding international research associate program.

Program analysis, two positions: Two positions are needed to obtain additional data necessary for program analysis. In order to make rational recommendations on NIH policies in support of overseas research additional data must be obtained and analyzed in relation to the economics of foreign countries and the impact of NIH programs.

International communications, two positions: Two positions are required to initiate the necessary exchange of medical and technical information in international research and to initiate studies leading to a solution of problems of communication flow between scientists, scientific organizations, and governmental organizations concerned with biomedical sciences internationally.

B. Training activities, increase of \$150,000.—An increase of \$150,000 and 10 positions is required for the recruitment of additional young scientists who will be assigned to ongoing research laboratories in overseas areas. The additional individuals upon completion of their 2½-year commitment will help to meet the increasing need for trained research individuals who are experienced in international medical problems.

INSTITUTE OF GENERAL MEDICAL SCIENCES

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research.....	\$63,929	\$70,715	\$6,786
Fellowships.....	14,077	16,260	2,183
Training.....	37,256	47,903	10,647
Total grants and related contracts.....	115,262	134,878	19,616
Direct operations:			
Review and approval of grants.....	2,145	2,561	416
Program direction.....	925	1,028	103
Total direct operations.....	3,070	3,589	519
Total estimate.....	118,332	138,467	20,135

1. Grants, increase of \$19,616,000

A. Research grants, increase of \$6,786,000.—1. Regular program increase of \$6,524,000:

1963 program-----	\$49, 313, 000
1964 continuations (type 5's and 2's)-----	38, 515, 000
1964 supplementals-----	2, 465, 000
1964 new projects-----	20, 920, 000
Additional indirect costs in 1964-----	3, 589, 000
Total need for 1964-----	65, 489, 000

At the close of 1963, it is anticipated that the backlog of approved but unpaid research projects will be negligible. On the basis of experience from the past several years, it may be predicted that new grant applications recommended for approval by the advisory groups will reach at least \$20,920,000 for 1964, an increase of about 20 percent in new applications over 1963, and that the requested amount for supplemental funds will be \$2,465,000. Although the President's budget is considered to be adequate to support the continuation of the established program, this requested increase in the funds for new grants will support the exploration of several promising areas of biomedical research. The additional funds will be devoted primarily to fundamental projects in those areas which are basic to the biomedical sciences. Such fields as biophysics, biomedical engineering, the development of new techniques and instrumentation, and a broader program in biochemistry and genetics will receive greater support than otherwise possible.

Increased emphasis will be placed upon the support of broad multidisciplinary programs which involve scientists working as coordinated groups within a given organizational framework toward the solution of broad, long-range problems. An effort will be made to increase research activity in pharmacology and toxicology, particularly in studies concerned with the mechanism of drug action, the effects of various chemical agents, and especially the effects of combinations of a variety of drugs and medicinals, on living systems and organisms.

Several of the emerging areas of research allied with the present program in the basic biomedical sciences will also receive increased attention. Studies in the behavioral sciences, for example, will lead to a better understanding of the interrelationships between men. The utilization of physical and mathematical models in the study of behavioral processes will be explored.

The estimated additional indirect costs of \$3,589,000 in 1964 is an increase of \$360,000 over the 1964 President's budget.

2. Scientific evaluation, increase of \$262,000

It is estimated that \$1,200,000 will be required in 1964 to support scientific evaluation grants. This is an increase of \$262,000 over the 1964 President's budget and is based on the establishment of new study sections to handle the expanded grants programs and also the requirements for increased site visits.

B. Fellowships, increase of \$2,183,000

1963 program-----	\$12, 964, 000
1964 increases:	
Regular fellowship program:	
Predoctoral-----	1, 615, 000
Postdoctoral-----	748, 000
Special-----	83, 000
Subtotal-----	2, 446, 000
Research career award program (including development awards)-----	850, 000
Subtotal-----	3, 296, 000
Total need for 1964-----	16, 260, 000

Although this program has experienced steady expansion, recent manpower studies have emphasized the need for still greater augmentation of the number of scientists trained for medical research. Additional funds requested for fiscal year 1964 will permit a reasonable expansion of support for research training of competent scientists in the basic biomedical and other health-related sciences, and particularly in such shortage areas as anesthesiology, biomedical engineering, biomathematics, medical genetics, molecular biology and experimental pathology.

The total requirement of \$16,260,000 estimated for all fellowship programs for 1964 represents an increase of \$3,296,000 over the \$12,964,000 available in 1963, and an increase of \$2,183,000 over the 1964 President's budget. An amount of \$9,504,000 is requested for the regular fellowship program to support increased numbers of candidates recommended by nationally recognized scientific leaders; this is an increase of \$1,333,000 over the 1964 President's budget for this program. The requested increase of \$1,615,000 for predoctoral fellowships will permit approximately 300 additional new awards in 1964, thereby bringing the total number of individuals supported in this category to 1200. In the postdoctoral program 110 additional fellows will be supported with the \$748,000 increase which is being requested, resulting in a program level of 370 awards. Similarly, the requested increase of \$83,000 for special fellowships will permit the support of 9 additional carefully selected and meritorious candidates for these awards, thus bringing the total number in 1964 to 74.

For the research career award program, an additional \$850,000 is being requested, bringing its total support to a level of \$6,756,000. The 1964 President's budget provided no increase in this program over the 1963 level (\$5,906,000). These additional funds will permit the continued growth of this successful program in 1964 by providing the increased numbers of stable career opportunities for scientists of superior potential and capability in the basic sciences related to health. Approximately 50 new awards can be made with the requested increase, thereby establishing a program level of 425 awards by the end of fiscal year 1964.

C. Training, increase of \$10,647,000

1963 program-----	\$33, 676, 000
1964 supplements to committed projects-----	5, 749, 000
1964 commitments-----	33, 676, 000
Approved but unpaid applications end of fiscal year 1963-----	1, 448, 000
1964 new projects-----	7, 030, 000
Total need for 1964-----	47, 903, 000

The total requirement for 1964 of \$47,903,000 represent an increase of \$10,647,000 over the 1964 President's budget of \$37,256,000. The proposed increase is based upon a very careful analysis of our various training grant programs in terms of needs for expansion in areas where manpower shortage is acute and in terms of supplementing present programs and initiating new ones. Although the increase allowed in 1963 approached over \$5.5 million, the Division of General Medical Sciences still lacked funds to pay high-quality, high-priority applications received from both medical and graduate schools, and recommended for approval by training committees and the National Advisory Health Council. With growing experience and improvement of facilities, training programs are gradually able to train more candidates. This increase in capacity, however, does result in a need for further funds, especially trainee stipends and equipment, which are sought through supplemental applications.

In fiscal year 1962, the supplementation rate was 16.9 percent. Applied to fiscal year 1964, this expansion of our training programs, which we consider a most efficient investment of the public funds, would amount to \$2 million more than the total increase allowed under the President's budget, or over \$5.7 million. The proposed fiscal year 1964 increase would not only fall short of the requisite amount to provide supplementation of present training programs, but would also make it impossible to meet nearly \$1.5 million in high priority approved unpaid applications held over from fiscal year 1963, and an anticipated \$7 million in new programs for which support will be recommended.

The \$7 million in new programs would permit major expansion in the field of behavioral sciences in accordance with the recommendations of the President's Science Advisory Committee. Emphasis would also be given to such extremely

important fields as computer research training and training in toxicology and clinical pharmacology. Continued emphasis on the training of candidates for research and faculty positions in the developmental sciences, multidisciplinary approaches to both the biological and medical sciences, and in genetics (especially human genetics) are also major program goals for which funds should be provided in 1964. If funds are available, training programs should also be initiated in the field of radiobiology, which is considered basic to research and academic positions in diagnostic radiology and radiotherapy.

2. Direct operations, increase of \$519,000

A. Review and approval, increases of \$416,000.—An increase of \$287,000 would provide support for 42 additional positions to administer the research, training and fellowship grant programs. These positions are required to: (1) respond to the greater need for grants management responsibility for the current program and (2) provide necessary and proper administration of the expanded grant programs requested in 1964.

An increase of \$129,000 is provided for payment to the NIH management fund.

B. Program direction, increase of \$103,000.—An increase of \$92,000 would provide support for 14 additional positions. Eight of these positions will be used in the Program Analysis Branch to permit the production of systematic data for program planning in the administration of grants. The remaining six positions would be used to strengthen the staff of the Institute Director.

An increase of \$11,000 is provided for payment to the NIH management fund.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants			
Research:			
Primate and animal resource centers.....	\$5,700	\$10,000	\$4,300
Special research resource centers.....	6,000	21,000	15,000
Communication centers.....		6,000	6,000
General clinical research centers.....	27,900	35,000	7,100
General research support grants.....	¹ (30,000)	¹ (40,000)	¹ (10,000)
Health research facilities construction.....	² (50,000)	² (150,000)	² (100,000)
Total, grants.....	39,600	72,000	32,400
Direct operations:			
Review and approval.....	986	1,729	743
Program direction.....	333	³ 810	477
Total, direct operations.....	1,319	2,539	1,220
Total estimate.....	40,919	74,539	33,620

¹ The general research support grants program is administered by this division and supported by each of the appropriations and not included in the total.

² The budget for health research facilities construction is a separate budget and not included in this total.

³ Includes \$300,000 for contracts for operation relating to program evaluation and standards for facilities.

1. Research grants, increase of \$32,400,000

A. Primate and animal resource centers, increase of \$4,300,000:

1963 program.....	\$5,120,000
1964 increases:	
1964 supplements.....	580,000
1964 new projects.....	4,300,000
Total, 1964 increases.....	4,880,000
Total need for 1964.....	10,000,000

The \$10 million will permit the establishment and support of other animal resource centers on an institutional, regional, or national basis, the development of a national effort to provide the types, quantities, and quality of animals needed for all areas of specialized biomedical research, and to establish standards of animal care.

**B. Special research resource centers and communications centers,
increase of \$21 million :**

1963 program-----	\$6, 000, 000
1964 continuations and supplements-----	6, 000, 000
1964 new projects:	
Special research resource centers-----	15, 000, 000
Communication centers-----	6, 000, 000
Total, 1964 new projects-----	21, 000, 000
Total need for 1964-----	27, 000, 000

This increase will provide specialized or unusual research facilities for instrument and electronic development, computing and scientific data processing, biomedical communication centers dedicated to management of health information and data, animal research and other research services in support of the institutional programs in the health-related disciplines. Some of the areas to be included are: Biomedical engineering, behavioral sciences, biostatistics, biomedical communications, tissue compatibility and organ transplantation, pharmacology and pharmaceutical chemistry, development and embryology, regulatory biology, physical methods in biology, marine biology, radiobiology, zoogeography, comparative biology, and study of trace metals.

C. General clinical research centers, increase of \$7,100,000 :

1963 program-----	\$33, 500, 000
1964 continuations and supplements-----	24, 900, 000
1964 new projects-----	10, 100, 000
Total need for 1964-----	35, 000, 000

The increase will support approximately 20 new centers. Program objectives are being achieved through awards to institutions such as medical schools and research hospitals for the establishment of special discrete research facilities centers and physical units or research wards (apart from the general care wards) with specialized supporting or core laboratory facilities and stable well-trained staffs. These will permit precise observations on patients and extend laboratory research in animals into valid correlative studies in human beings. The units are available for multicategorical and multidepartmental research, in which preclinical and clinical scientists with a variety of research interests and techniques share the special facilities.

D. General research support grants (increase of \$10 million. Supported by each of the NIH appropriations and administered by this Division) :

1963 program-----	\$30, 000, 000
1964 program-----	40, 000, 000
Total need for 1964-----	40, 000, 000

The general research support grants program is supported by each of the NIH appropriations. Reports and program information obtained indicates conclusively that institutions receiving these funds are already reaping benefits in many ways. The increase of \$10 million will help the institutions to develop well balanced research and research training programs.

*E. Health research facilities construction (increase of \$100 million).—*The Division of Research Facilities and Resources is responsible for the administration of the health research facilities construction program. The budget for the health research facilities construction is a separate budget and shown elsewhere.

2. Direct operations, increase of \$1,220,000

A. Review and approval, increase of \$743,000.—An increase of \$743,000 and 61 additional positions will be required to support the professional and clerical staff needed for the expanded research grants program and health research facilities construction program.

B. Program direction, increase of \$477,000.—An increase of \$477,000 and 10 positions will be required for the overall planning, direction, and coordination of the programs of the Division of Research Facilities and Resources. This increase includes \$300,000 for contracts for operation relating to program evaluation and standards for facilities.

NATIONAL CANCER INSTITUTE

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Change
Grants:			
Research.....	\$65,253	\$73,530	+\$8,277
Fellowships.....	5,188	4,100	−1,088
Training.....	12,520	8,970	−3,550
Total grants.....	82,961	86,600	+3,639
Direct operations:			
Research.....	17,241	17,500	+259
Collaborative studies.....	42,120	56,570	+14,450
Review and approval.....	1,969	2,019	+50
Program direction.....	823	873	+50
Total direct operations.....	62,153	76,962	+14,809
Total estimate.....	145,114	163,562	+18,448

1 Grants, increase of \$3,639,000

A. Research, increase of \$8,277,000.—An increase of \$4,870,000 over the President's budget would provide support for the normal increases in continuations, supplementals, and new grants, based on the relationship of 1963 estimated amounts and the 1962 actual. An increase of \$2,900,000 for programed chemotherapy grants represents a transfer of \$1,700,000 from contracts and a program increase of \$1,200,000. Additional clinical trials will be initiated to cover the expected substantial increase in the volume of drugs becoming ready for trial and to place greater emphasis on evaluation of therapeutic response achieved with active materials, in addition to continuation of comparative studies underway. An increase of \$100,000 would provide for scientific evaluation and planning grants for increased work by committees in evaluating proposed research and appraising progress in the cancer field. An increase of \$407,000 would be required to cover the approximate additional 5 percent in indirect costs on the above increases for grants awarded after January 1.

B. Fellowships, decrease of \$1,088,000.—There is currently a decrease in NCI postdoctoral and special awards due to a change in the character of applications with a reduction in those appropriate to the cancer field. Since the preparation of the 1964 estimates records of the 1963 applications have become available, which, when used as a basis for projection into 1964, would reflect a need for about \$600,000 less than is presented in the President's budget. It is estimated that the career awards program will require about \$488,000 less than is presented in the President's budget. This program is relatively new and at the time the 1964 estimates were prepared we did not have sufficient experience in the current year to project accurately the needs. These proposed amounts represent increases over estimated 1963 expenditures of \$1,045,000 for regular fellowships and career awards.

C. Training, decrease of \$3,550,000.—Since the preparation of the 1964 estimates a study of training support needs has been made based on current 1963 experience. This study reveals that many training directors have extended their programs beyond cancer research and have broadened their requests in some cases to obtain support for multicategorical and multidisciplinary programs from the National Institute of General Medical Sciences. This has resulted in a reduction in expectations for requests for Cancer Institute funds in 1964. Latest experience also shows that some programs, such as those in pharmacology of long-term, low-level exposure to chemicals, clinical laboratory medicine and carcinogenesis, have not reached stages of development that will yet require the additional support anticipated. The proposed amounts represent increases over estimated 1963 expenditures of \$760,800 for training grants.

2. Direct operations, increase of \$14,809,000

A. Research, increase of \$259,000.—An increase of \$50,000 would provide for increased use of computers in laboratory and clinical research problems—a development of growing significance in current research efforts. An increase of \$209,000 would provide for expansion of laboratory medicine efforts, including the introduction of automated procedures for chemical and other types of tests on materials derived (e.g., blood, serum, cells, urine, etc.), with regrouping of staff and resources and the possible establishment of a new Laboratory of Experimental Clinical Pathology.

B. Collaborative studies, increase of \$14,450,000.—1. Field studies, increase of \$1 million: This increase would provide for epidemiologic studies related to virus antibody patterns in defined populations, including individuals who have received a variety of vaccinations. Some of these studies will be in conjunction with the program of the recently established Human Cancer Virus Task Force which is concentrating on evaluating the role of viruses in human cancers, especially leukemia.

2. Diagnostic activities, increase of \$150,000: This increase would be used to support the expansion of Diagnostic Research Branch staff and facilities to provide for the growing needs of coordinating the various program segments as the total diagnostic research efforts have evolved, including greater use of automatic data processing to maintain surveillance and review of cancer diagnostic research data, published literature, and the current research contract program.

3. Carcinogenesis and virus activities—"No-year account," \$15 million: During the next several years primary buildup will continue in program areas of carcinogenesis studies and cancer virology. Expanded efforts have been made through the grants mechanism and in research conducted in intramural laboratories with considerable success, and such avenues of increased support will continue. A modest supplement to those efforts has been made through the contract mechanism. However, program developments in these two areas will require entirely new mechanisms of research effort and facilities and other resources not now in existence, and large increases in funds will be required. Considerable sums of money will be required for such items as a large-scale serum bank, housing specimens collected from defined, large populations of individuals who must be followed for considerable periods of time and large numbers of a variety of animals with special characteristics. In addition, large amounts of funds will be required for the facilities necessary for maintaining these animals, some of which will be infected with hazardous viruses, and for exposing animals to controlled atmospheres containing known and potential cancer-causing agents.

Since these programs are large and complex, and require integration and coordination difficult, if not impossible, to achieve through the customary grants and intramural laboratory programs, a series of interrelated contracts with industry and cancer research is needed. These contracts will often be of considerable magnitude and will need to provide for complex facilities. A key feature is the inclusion of at least one major facility operated by a contractor with experience and capabilities required for developing facilities and staff and for carrying out complex programs formulated and generally supervised by senior program Institute staff. Such an organization and facility could be rapidly modified as program needs change.

To develop this research approach in the carcinogenesis and virology areas will require a period of a few years and may require modification of existent authorities. A sum of \$15 million of "no year" moneys would permit moving ahead with this approach for strengthening cancer research.

4. Chemotherapy activities, decrease \$1,700,000: This decrease reflects the transfer of funds from chemotherapy contracts to programed chemotherapy grants referred to under 1.A. above.

C. *Review and approval, increase of \$50,000.*—This increase will enable the Institute to conduct more effectively the expanded grant management program activities especially through added data analyses.

D. *Program direction, increase of \$50,000.*—Additional communications responsibilities are being added to the Institute's functions, and this increase would permit increase in these efforts.

3. *Reimbursements to the NIH management funds have not been considered in this document beyond the level reflected in the President's budget*

MENTAL HEALTH ACTIVITIES

1964 President's budget and professional judgment budget

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
(a) Research.....	\$80,755,000	\$80,755,000	0
(b) Fellowships.....	8,534,000	8,534,000	0
(c) Training.....	66,048,000	66,048,000	0
(d) State control programs.....	10,950,000	10,950,000	0
Direct operations:			
(a) Research.....	10,608,000	10,608,000	0
(b) Collaborative studies.....	4,363,000	4,363,000	0
(c) Training activities.....	1,001,000	1,001,000	0
(d) Professional and technical assistance.....	3,998,000	3,998,000	0
(e) Review and approval of grants.....	3,234,000	3,234,000	0
(f) Program direction.....	605,000	605,000	0
Total appropriation.....	190,096,000	190,096,000	0

NATIONAL HEART INSTITUTE

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research.....	\$97,183	\$99,532	\$2,349
Fellowships.....	6,399	7,500	1,101
Training.....	15,179	15,179	0
Total, grants.....	118,761	122,211	3,450
Direct operations:			
Research.....	10,608	11,030	422
Collaborative studies.....	1,426	2,000	574
Training activities.....	250	250	0
Review and approval.....	2,183	2,411	228
Program direction.....	396	459	63
Total, direct operations.....	14,863	16,150	1,287
Total estimate.....	133,624	138,361	4,737

EXPLANATION OF INCREASES

The 1964 President's budget for the National Heart Institute reflects several significant changes from budgets submitted for 1963. The primate center program has been transferred from NHI to the Division of Research Facilities and Resources and the NHI State control and professional and technical assistance

programs have been transferred to the Bureau of State Services. These transfers affected a considerable reduction in the base amount of NHI's budget. Considerable increases were allowed for the research, fellowship award, and training grant programs in 1963 and are provided in the 1964 President's budget. With these factors in mind, as realistic an assessment as possible has been made of the future direction of NHI's various programs, both for grants and direct operations. This professional judgment budget reflects, in monetary terms, the goals that are deemed worthy of accomplishment by NHI program officials. This budget projects relatively conservative increases when compared with budgets of previous years. This, in turn, reflects a more realistic President's budget this year as well as due consideration given to what can be programed both by the Heart Institute and its grantee institutions during the coming year. It is felt, however, that certain increases over the President's budget are both realistic and desirable. The most significant of these needs are (1) to increase the continuation and supplemental ratio for research grants based on past years' experience, (2) to expand the accomplishments made in the career fellowship award program, (3) to bring the direct intramural research effort to an adequate operating level, and (4) to provide for the cardiovascular research opportunities being afforded through collaborative studies.

1. Grants, increase of \$3,450,000

A. Research grants, increase of \$2,349,000.—The total increase would be applied to continuation and supplemental requirements. Experience over the past 3 years indicates that a ratio of 94 percent for these requirements compared with the total regular program of the previous year has been necessary. The requested increase would provide for this percentage ratio. An important factor which influences this level of grant continuations is the National Advisory Heart Council's inclination to recommend the first year award level of a new grant with an expressed or implied commitment for greater support in subsequent years.

B. Fellowships, increase of \$1,101,000.—The increase requested would be used entirely to provide support for 59 additional career award and career development awards in 1964. It is not expected that the numbers of postdoctoral and special fellowship approvals would exceed the amount provided in the President's budget.

2. Direct operations, increase of \$1,287,000

A. Research, increase of \$422,000.—This increase is based on the following five considerations: (1) The increased cost and usage of blood; (2) the need for more surgical supplies related to the opening of the new surgical suite as well as for ancillary basic surgical research. Particularly relevant is the increased use of dogs and the development of instrumentation for surgical research; (3) the need to reduce lapse rates for positions in the established program because of gradual upgradings and lack of turnover in both civil service and commissioned positions; (4) a minimal increase of 6 percent to cover inflationary costs to meet the going rate of expenditures for supplies, materials, etc., in the individual laboratory budgets; (5) the need to establish a recurrent equipment budget for the replacement of wornout and obsolete equipment.

B. Collaborative studies, increase of \$574,000.—This increase would be used to fill major gaps in professional competencies and laboratory resources needed to bring multidisciplinary research techniques into studies of the natural development of heart disease in human and animal populations. It would provide for a sizable expansion of research personnel and activities in the geographical diseases area. While the increase would be used to agument a variety of collaborative projects, it is particularly important to concentrate on (1) the expansion of an existing nucleus of collaborative effort in pathology and comparative pathology. This is urgently needed to take advantage of diverse opportunities for learning about differences in cardiovascular disease within the human and animal populations in which collaborative epidemiological studies already exist. (2) A laboratory of medical nutrition and food chemistry would be established to give intensive study to the role of dietary factors in cardiovascular disease. A revolutionary change in American dietary practices is gaining momentum, yet the Heart Institute has no senior research competence in medical nutrition to participate in collaborative research and to provide advice in this extremely important area. (3) Both genetics and biochemistry groups would be established to fill the specific needs of population studies already in progress as well as those newly developing. The Heart Institute does not have

scientists in these specialties participating in its cardiovascular epidemiology studies. (4) A research group to develop measures for physical energy expenditure for use in different population studies would be formed. This group would help to clarify the suspected role of physical activity and physical fitness in relation to coronary heart disease. (5) The general program would also be strengthened to provide competent researchers in the social sciences for participation in population studies.

C. Review and approval, increase of \$228,000.—Provision is made for additional staff (1) to facilitate the review and approval of the expanded grant programs, (2) to provide a more detailed and sophisticated review and analysis, and (3) to meet the need for effective management of grants.

D. Program direction, increase of \$63,000.—This increase is necessary to provide for the appointment of an Associate Director for Scientific and Technical Communications and the staffing of such an office for biomedical communications as recommended by the Surgeon General's Biomedical Communication Conference.

National Heart Institute

[In thousands]

	1964 President's budget	Professional judgment budget	Increase
Research grants:			
1. Continuations and supplementals.....	\$65,921	\$68,270	+\$2,349
2. New grants.....	18,634	18,634	0
3. Additional indirect costs.....	4,896	4,896	0
4. Subtotal.....	89,451	91,800	+2,349
5. General research support grants.....	6,107	6,107	0
6. Categorical clinical research centers.....	1,600	1,600	0
7. Scientific evaluation and planning.....	25	25	0
8. Total.....	97,183	99,532	+2,349

	Average cost	1964 President's budget		Professional judg- ment budget		Increase	
		Number	Amount	Number	Amount	Number	Amount
Research fellowships:							
Postdoctoral.....	\$7,000	439	\$3,073	439	\$3,073	0	0
Special.....	9,966	118	1,176	118	1,176	0	0
Career awards.....	18,696	115	2,150	174	3,251	+59	+\$1,101
Total.....		672	6,399	731	7,500	+59	+1,101

	1964						Increase		
	President's budget			Professional judgment budget					
	Number	Trainees	Amount	Number	Trainees	Amount	Number	Trainees	Amount
Training grants:									
Undergraduate-----	104		\$2, 451	104		\$2, 451	0		0
Graduate-----	343	1, 544	12, 718	343	1, 544	12, 718	0	0	0
Scientific evaluation-----			10			10			0
Total-----	447	1, 544	15, 179	447	1, 544	15, 179	0	0	0

NATIONAL INSTITUTE OF DENTAL RESEARCH

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research.....	\$9, 833	\$10, 452	+\$619
Fellowships.....	1, 257	1, 500	+243
Training.....	4, 805	4, 805	-----
Total grants.....	15, 895	16, 757	+862
Direct operations:			
Research.....	3, 200	3, 799	+599
Collaborative studies.....	0	545	+545
Review and approval.....	529	641	+112
Program direction.....	185	377	+192
Total direct operations.....	3, 914	5, 362	+1, 448
Total estimate.....	19, 809	22, 119	+2, 310

1. Grants, increase of \$862,000

A. Research, increase of \$619,000.—The increase requested would provide additional support in the following fields (new grants and supplemental requests) :

1. Congenital anomalies research.....	\$150, 000
2. Behavioral sciences research.....	100, 000
3. Dental restorative material research.....	150, 000
4. Other research (dental caries, salivary studies, neurophysiology, calcification, growth and development, and dental public health investigations).....	150, 000
5. General research support.....	69, 000
Total.....	619, 000

B. Fellowships, increase of \$243,000.—The increase would provide \$80,000 to support 11 additional postdoctoral fellowships to provide advanced training in research, including clinical investigations; \$43,000 to support 5 additional special fellowships to provide further specialized research training; and \$120,000 to support 6 additional research career award fellowships.

2. Direct operations, increase of \$1,448,000

A. Research, increase of \$599,000.—Of this increase, \$60,000 would be provided for 5 additional positions in the microbiology program in order to expand research in immunology and bacterial physiology, gnathobiotics, and the virus program; \$136,000 would be allocated to the biometric and epidemiological program for 5 positions, and the cost for data processing in a program of increased needs related to expanding biological research in genetics and for further exploitation of laboratory leads developed relative to the infectious and transmissible nature of dental caries and the physiology of fluorides; \$80,000 would support 6 new positions in the biochemistry program to expand research activities in experimental animal caries, and protein and enzyme chemistry; \$117,000 would provide for expansion in the histology and pathology program to support 6 new positions in research related to the crystal structure of bones and teeth, and the histochemical and morphological characteristics of connective tissue in aging and disease; \$42,000 would be for the support of 3 positions in the Office of the Associate Director; and the remaining \$164,000 represents an increase to the NIH management fund for centrally furnished services.

B. Collaborative studies, increase of \$545,000.—This budget proposes the establishment of a collaborative studies activity in the National Institute of Dental Research budget. It is felt that this action is necessary (1) to permit the trans-

fer of funds necessary to support specific dental research projects to profit-making organizations since these are now to be financed through the contract mechanism rather than grants, and (2) to expand research in the development of dental restorative materials as proposed by the National Advisory Dental Research Council and an ad hoc committee of outside consultants. This latter program would be carried out through contracts with researchers, grantees, and other Government agencies. The increase would provide \$500,000 for expansion of basic and clinical research in the field of dental restorative materials and related therapeutic agents; and \$45,000 to support three positions with responsibility for central leadership and control.

C. Review and approval of grants, increase of \$112,000.—The increase requested includes \$77,000 which would provide eight additional staff to administer the increased grants program and for extension of grants management functions. Also, an increase of \$35,000 represents payment to NIH management fund for centrally furnished services.

D. Program direction, increase of \$192,000.—Of the increase requested, \$157,000 would provide for an extensive program in analysis and review of operations, and initiation of a scientific and technical communication office to plan activities for the use of information derived from research and training activities, as well as from direct research operations. An increase of \$35,000 would permit payment to the NIH management fund for centrally furnished services.

ARTHRITIS AND METABOLIC DISEASE ACTIVITIES

Professional judgment budget, fiscal year 1964

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research.....	\$82,513	\$86,754	\$4,241
Fellowships.....	4,019	6,750	2,731
Training.....	14,420	15,260	840
Total grants.....	100,952	108,764	7,812
Direct operations:			
Research.....	11,307	11,469	162
Collaborative studies.....	713	713	0
Review and approval.....	1,469	1,495	26
Program direction.....	276	310	34
Total direct operations.....	13,765	13,987	222
Total estimate.....	114,717	122,751	8,034

RESEARCH PROJECTS

The establishment and continuation of a strong, multifaceted attack on arthritis, diabetes, and other metabolic disorders and the remainder of its categorical responsibilities continue to be the cornerstone of the Institute's extramural activity. The estimate permits reasonable expansion of types of studies which have proven to be productive while concomitantly allowing the encouragement of new approaches having sufficient potential to justify the investment of funds. The varying types of grants awarded or under consideration in the area of peptic ulcer provides an excellent example of this concept. For a number of years the Institute has been supporting a growing variety of studies oriented toward a better understanding of the physiology and pathology of the gastrointestinal tract. Only a portion of these directly involve ulcers but all are capable of producing badly needed new knowledge which could be important to that area. This growth has enabled new types of investigators to bring to bear previously unavailable techniques and information. Recently, one of these unusual approaches produced a new treatment

for peptic ulcer—that of freezing the stomach mucosa for short periods of time. The initial reports on its use in humans have been highly encouraging. Additional evaluation of the procedure, however, is definitely necessary before the medical community can, with real assurance, accept or reject the technique as suitable for mass application. The Institute, therefore, has moved on two fronts in this matter. The grant which supported the original work continues and proposals for a cooperative study of the new technique in several other institutions are now being reviewed. Thus, an unequivocal answer as to its true value would be made available. Of potential value is the probability that these investigations will also provide new knowledge about the nature and development of peptic ulcer itself.

The situation described above can and should be replicated in the many categorical areas for which the Institute has responsibility. The availability of funds determines, to a great extent, whether or not all possible approaches to the acquisition of new knowledge will be exploited. The sum mentioned above is that which appears to be necessary for the proper, well-balanced growth of the NIAMD research grant program.

FELLOWSHIPS

The NIAMD (National Institute of Arthritis and Metabolic Diseases) fellowship program is essential to its training activity in terms of complementing the larger graduate training grant program. The latter has been purposely restricted to clinical departments for the post-doctoral training of physicians in research and the acquisition of advanced clinical skills. The fellowship provides support then in those circumstances where a training grant would not be feasible or appropriate. Thus, the NIAMD postdoctoral fellowship enables the Ph. D. biochemist or physiologist to gain additional training focused on disease problems in metabolic diseases. It also permits the M.D. to gain valuable experience in a particular situation where no training grant funds are available. The special fellowship, on the other hand, becomes an increasingly valuable tool because of its great flexibility. It may enable a superior technician to acquire skill in a new technique by spending several months in another laboratory. A seasoned investigator can increase his scientific productivity by bringing up to date his training in established or newly developed areas. Still a different usefulness is the "topping off" training so frequently necessary between post-doctoral or traineeship experience and a man's initial academic appointment. Much of the additional sum recommended in this activity would be utilized in these two areas.

Increases are also in order for the two levels of the research career award program. This program is considered one of the most significant additions in extramural activities in recent years. By this device the most promising younger individuals and the recently established independent investigator may be given some measure of assurance as to stability of income, a highly important factor in increasing the scientific manpower pool. Because of its variety and number of categorical responsibilities, the NIAMD receives an unusually large number of excellent applications for these awards. The additional funds in this area would permit the growth of this activity at a reasonable rate.

TRAINING GRANTS

The proposed expansion of the Institute's graduate training grant program follows the plan as developed in fiscal year 1963. This was predicated on a pattern extending over a 2- or 3-year period with the following components:

1. The strengthening of selected presently supported training centers through extending the period of stipend support beyond the current average of 15 months.
2. The establishment of new training centers in carefully selected situations. Although this would involve all of our program areas to a limited degree, it would emphasize a few areas such as orthopedics and renal disease where needs are greatest.

3. The expansion as planned of the original centers in the experimental program for training of clinical investigators and the addition of a few new centers. This activity holds particular promise for significant increases in both the quality and quantity of investigators at the clinical level by encouraging frank innovation in the training of such individuals. By placing these grants in highly selected environments, full advantage can be taken of a depth and breadth of academic resources considered essential for best development of this undertaking.

The additional funds mentioned above are necessary if this essential component of the Institute's program is to continue its orderly growth.

If the research activity so successfully developed at the present time is to maintain its productive momentum in future years, attention must be focused on current training needs. The components described above are designed to make maximal use of resources presently available while also attempting to use those resources more efficiently in the years ahead.

Research, net increase \$162,000

Great advances have been made in recent years in our knowledge and understanding of the biochemistry of genetics. The chemical nature of a gene (namely, the sequence of nucleotides (RNA) necessary for synthesis of a specific protein chain) has been determined. When genetic material is altered in one of several ways (deletion, duplication, translocation, inversion), mutation follows. Mutation is responsible for hereditary molecular diseases. "Inborn errors of metabolism" are molecular diseases in which discrete mutations have caused failure of an enzymatic reaction. NIAMD has been directly engaged, for many years, in elucidating the biochemical lesions in hereditary metabolic diseases. New methods and elegant techniques in microbial and human genetics, some of which have been developed in the laboratories of NIH at Bethesda (such as cytogenetics, growth of human cell lines on tissue culture), have now opened new doors. These leads should be vigorously and promptly pursued with the aim of gaining a deeper insight into the nature of these ever-increasing disorders, of their early recognition and diagnosis, and of developing successful treatment or prevention in the diseases where such measures seem feasible and promising. In particular, hereditary metabolic diseases are now realized to be much more common than previously suspected. There is now, for example, evidence that one out of two individuals carry a recessive gene for a serious disease.

Newer concepts of immunology, of immunological tolerance, of synthesis of various types of antibodies, and of the host response to antibodies and antigen-antibody complexes, have led to an increasing awareness of autoimmunity as a basis for certain diseases in man. Many of these diseases have been subjected to intensive studies in the laboratories of NIAMD in Bethesda, such as hemolytic anemia thrombocytopenia, Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome. Significant and original observations were made and reported in two of these diseases in our laboratories in the last 2 years. These studies should be extended with minimal delay.

The requested increase includes 10 research positions and \$140,000 for acceleration of the above-described studies, and 3 positions and \$22,000 to strengthen scientific report writing and scientific communications requirements.

Review and approval, net increase \$26,000

The requested increase, along with 10 additional positions, would provide what is considered minimal staffing for effective grants administration, with emphasis on reviews in depth of grant applications and continuing scrutiny of ongoing projects.

Program direction, net increase \$34,000

This activity is the Director's immediate staff, responsible for general administration of the several Institute programs. The requested increase is needed to support personnel authorized in 1963 for which adequate funds were not provided.

ALLERGY AND INFECTIOUS DISEASE ACTIVITIES

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research.....	\$40,628	\$56,465	\$15,837
Fellowships.....	3,058	5,500	2,442
Training.....	7,992	9,550	1,558
Total, grants.....	51,678	71,515	19,837
Direct operations:			
Research.....	10,931	13,556	2,575
Collaborative studies.....	5,284	9,047	3,763
Review and approval of grants.....	992	1,165	173
Program direction.....	291	522	231
Total, direct operations.....	17,548	24,290	6,742
Total estimate.....	69,226	95,805	26,579

1. Research and related activities, increase of \$19,837,000

A. *Research grants, increase of \$15,837,000.*—1. Regular program, increase of \$14,478,000: The NIAID research grants program will have a significant deficit for the support of regular research project applications approved by the Council for payment in 1963. It is a safe prediction that most of the established productive investigators whose projects were approved but could not be supported, will submit their applications for essentially the same projects for reconsideration in 1964. The funding of this backlog would require approximately \$3 million over and above the normal increase in new applications for the coming year.

This Institute has initiated a program of active promotion of research in long neglected and rapidly expanding areas of prime categorical interest. Preparation to support these areas has been made through increased programing activities of the extramural staff and the anticipated dividends which should result from the recent development of the Institute's research training and career award programs. Numerous large research grant applications which have been programed with active staff participation are expected to pass through scientific review and be approved for support by 1964. A few examples are listed below with their approximate annual cost of support: a large project at Baylor University in the Department of Virology, \$200,000; a grant in the field of tropical medicine in Panama, \$150,000; a project in allergy at Columbia University, \$100,000; a grant in immunology to a principal investigator at Washington University in St. Louis, \$100,000; a grant in insect pathology at the University of California, \$180,000; and a project in organ transplantation at Harvard Medical School, \$100,000. The total need for additional support of the regular research grant program is predicated on the intensified programing effort described above, an anticipated continued increase in worthy applications at the same rate as in the past, and the backlog of unsupported applications from prior years. Additional scientific evaluation funds will also be needed to sustain these functions.

Several areas of great potential growth require special attention.

Virology: An acceleration of activity is expected due to several reinforcing factors, including recent development of efficient new methodologies, increases in the magnitude and competency of scientific manpower in virology and related areas, and the establishment of new facilities and the availability of material resources. In addition, potentially highly rewarding research on viral chemotherapy will receive increased programing emphasis.

The rapid development of new concepts, procedures, and instrumentation gives this whole area an aura of expectation. Research in cytology, genetics, enzymology, bioorganic chemistry, and biophysics has been effectively brought to bear on the nature and characterization of viruses and of viral invasiveness and

proliferation. The availability of new research facilities and well-trained manpower and the augmenting effect of viral reference reagents will increase productivity greatly.

Research in virology is expensive and time consuming. Most laboratories doing research on viruses require a number of specialists at both the technical and professional levels. Instruments are complex and expensive to purchase, install, and maintain.

Immunology and immune mechanisms: In addition to seeking new leads for vaccine development and enhancement of host immunity, the possibility of influencing and manipulating immune mechanisms has enormous research potential for allergic disorders, a number of little understood chronic diseases, and tissues and organ transplantation. The growing awareness of this potential is generating a demand for increased support.

Allergic and related disorders: Allergies are assuming greater importance as other acute and chronic disorders respond to enlightened therapy. It is confidently expected that within the next few years demands for a greater research effort in this area will be heard.

A major programing effort is underway in allergic and immune mechanism disorders. Although several years will be required to develop a substantial program, funds to be spent in 1964 will provide the impetus, and demonstrate the intention, of this Institute to assume greater responsibility for research in this area.

Bio-organic chemistry: Of increasing concern to this Institute is the incapacity of present day biochemistry to provide for follow through in relating molecular structure to biological function in areas of interest to the NIAID. It is our intention to assist in developing specialized centers for cooperative research on analogs of enzyme substrates and subcellular components that might logically be expected to interfere with virus reproduction; bacterial and fungal metabolism, and to effect immunological mechanisms. The potential for developing such centers is within our grants program at present.

Bacteriology: Basic research on the identification, pathology and treatment of refractory bacterial, mycotic, and parasitic diseases will be continued with a high order of priority.

Tropical medicine, zoonotic, and related diseases: Tropical fauna is now known to harbor a number of transmissible disease agents common to both animals and mankind. Some of these agents are readily transported by flying insects and migratory birds. There is evidence to support the hypothesis that secondary disease reservoirs in temperate regions are being established and replenished from the vast reserve in the tropics. Thus we are confronted with problems which relate climatology, zoology, entomology, and infectious diseases on a grand scale and point to the need for developing a series of cooperative research laboratories through the United States, Central America, and the countries of northern South America. These facilities would reinforce one another in a long-range program to determine the factors that favor the periodic resurgence of these diseases and develop more precise and effective measures for checking the proliferation or transmission of them. The trend toward programed projects is expected to continue and accelerate. Active programing will be carried on to encourage this trend toward longer term, more flexible support of established research activities in laboratories with demonstrated productivity. Program projects will most often carry commitments for support at a level which permits orderly growth, and supplementation must be anticipated as new areas of productive research open up.

In the regular program, expenditures for new and continuing research grant support increased from 1961 to 1962 by slightly over \$4 million. The support of new grant applications approved by Council in 1962 and 1963 would increase the continuation requirement for 1964 by a proportionate amount. This projection is subject to several variables which will influence the level of continuation support in 1964:

(a) With the shift in emphasis from passive application acceptance to active program promotion, a number of small project grants in the regular program will be absorbed and terminated upon the award of new program-oriented projects.

(b) The 1963 appropriation will permit the award of only two-thirds of anticipated new and supplemental approvals which would ordinarily require continuation support in 1964. These fund limitations have prompted the National Advisory Allergy and Infectious Diseases Council to disapprove a

considerable number of applications favorably recommended by study sections but, with relatively poor ratings. Such applications are removed from the list of applications eligible for payment.

To permit implementation of programed project activities in 1963 it will be necessary to carry over approximately one-third of the approved but unpaid grants in the regular program. It is expected that funding of program projects will tend to slow the rate of new regular projects, but this will be partially offset by increased availability of manpower and facilities available for the conduct of research.

The rate of increase in the amount required for each succeeding year for currently supported program projects will exceed the previous year's rate of increase in expenditures for continuations, supplements, and new grants. This is due to the fact that attrition for the large programs is negligible and the growth over the next 10 years is potentially high.

2. *Special programs, increase of \$1,359,000*

The Gorgas Memorial Laboratory will move into its newly enlarged quarters during 1963. The expanded activities will require an additional \$250,000 in 1964, the first full year of operation on a broader scale.

An increase of \$500,000 is needed for the clinical research centers program to meet this Institute's commitment to develop a long-range program of clinical research in chronic disorders involving the immune mechanisms, such as allergy, asthma, and a number of poorly defined illnesses that indicate hypersensitivity to internal or external stimuli. Progress in tissue and organ transplantation depends on suppression of the immune reactions. This kind of research requires extensive long-term clinical observation which can be best undertaken in such a center. That a number of virus diseases have a chronic as well as an acute phase has become fully apparent and this fact bears importantly on the problem of securing information about the processes involved in the development of these chronic infections.

An increase of \$584,000 will provide additional funds for this Institute's share of the centrally administered general research support grants program.

B. Fellowships, increase of \$2,442,000.—The number of new postdoctoral fellowships which can be awarded in 1964 is limited due to recent increases in the average stipend level and the modest increase provided in the 1964 President's budget. Additional funds in this category would provide for the award of all applications which are judged by review groups to be outstanding.

A small increase above that presently in the budget could be effectively programed for special fellowships. The traditional purpose of this category is to provide opportunities for established investigators to develop new skills and competency in selected research areas. In 1963 and 1964, an increased number of these awards will permit the Institute to engage in an active recruitment program. Positions will be reserved for well-qualified clinicians who wish to pursue careers in research and teaching in clinical allergy and infectious diseases and well-established investigators who can be induced to initiate or organize research programs in underdeveloped institutions, either within or outside the United States. Awards are made to support well-known scientists who wish to spend a sabbatical year in other laboratories. Nominations will be sought from training program directors, sponsors of large contingents of fellows, and other likely sources.

The vast majority of research career awards and research career development awards are awarded with long-term moral commitments. As of December 1962, approximately 85 percent of the total awards provided in the 1963 budget carried commitments through 1964 or later. Based on past experience, a considerable increase in funds could be utilized for new awards in 1964.

C. Training grants, increase of \$1,558,000.—In step with the active promotion of research in neglected and in rapidly expanding areas of prime concern to the NIAID, the training grant programs will provide the means to build more effectively for the long pull. In some areas such as allergy and related chronic disorders real progress is heavily dependent upon development of new trained research personnel. The demand for virologists and immunologists cannot be effectively met at present because of the rapid expansion in these areas.

The inability to deal effectively with a growing number of refractory bacterial diseases points up the need for more imaginative and extensively trained research personnel. These ends can be accomplished through the provision of additional funds for scientific evaluation grants and the graduate training program.

2. *Direct operations, increase of 103 positions and \$6,742,000*

A. *Research, increase of 57 positions and \$2,575,000.*—Respiratory virus research, increase of 22 positions and \$545,000: These increases are needed to expand staffing and facilities to support a realistic program for respiratory diseases research including the much-publicized common cold. Recent reports in magazines and journals and official releases imply that an all-out effort is being made to produce early results in this area; however, the present operating level is not sufficient to justify this current optimism. In virus research, the discovery of the new agents is proceeding so rapidly that in many cases the scientists are finding it impossible to do much more than identify and classify them. The more important work which still needs to be done is to attempt to identify the specific agents with known symptoms of a particular illness. Although viruses or pleuropneumonia-like organism (PPLO) are implicated in about 60 percent of serious respiratory illnesses in children, the complexity of the isolation and propagation of these agents requires the development and use of new tissue culture preparations and methods. Of the increase approximately \$142,000 is needed for salaries and \$268,000 for travel, equipment, animals (including primates) and supplies and materials; \$135,000 is needed to purchase the high-quality tissue cultures used in this work through contracts with commercial firms.

Virus identification and cancer studies, increase of 18 positions and \$720,000: This program was established as a collaborative effort in 1962 with the National Cancer Institute to assist in the coordination of investigations on viruses as a cause of cancer in animals and in man. During the past 2 years, this unit has been supported by the Cancer Institute. Of the increase requested, nine positions and \$538,000 will permit placing this activity in the proper organizational unit and make it self-supporting. It will also permit the rapid application of recently developed virologic techniques to the study of tumor viruses. Funds will provide expansion of laboratory facilities and provide diagnostic antisera and antigens from commercial sources. The nine new positions and \$182,000 are needed to provide supporting staff for senior investigators now on duty and additional tissue cultures, reagents, animals and equipment for the serological studies involving nearly 100 human viruses, many mouse viruses, including polyoma and diseases of rabbits and chickens. The magnitude of the specimen testing to define and eliminate extraneous viruses from cancer virus systems taxes the present resources of this unit and precludes rapid application of newly developed techniques for investigations into the broader role of viruses in cancers.

Epidemiology of infectious diseases, increase of six positions and \$102,000: The increase under this heading will provide for expansion of investigating the epidemiology of infectious diseases as they concern viral diseases, specifically enteroviruses, reoviruses, adenoviruses, myxovirus and respiratory syncytial virus. Three positions and \$30,000 will be used to expand studies at Junior Village in Washington, D.C., for field trials of vaccines designed for use in children. Three positions and \$52,000 will be used to complete the staffing of the Pacific Research Section, located in Honolulu, Hawaii, where studies on eosinophilic meningitis and other diseases of particular importance to Hawaii, American Samoa, and other islands in the Pacific area; \$20,000 will be used to provide increases for travel, supplies and materials and equipment for current epidemiological field studies of infectious diseases as they occur in various population groups.

Special studies, increase of 11 positions and \$412,000: Certain neurologic diseases and collagen (protein of connective tissues) disorders of man seem to have counterparts in animal diseases such as scrapie (a chronic infection of sheep caused by a virus), Aleutian mink disease, and others. Animals offer the best means for research into the obscure causes of apparently similar diseases in man, in whom long-term studies can be carried out only with great difficulty and expense. In order to utilize the comparative-pathology approach to an understanding of the role of viruses in chronic illnesses of man, special facilities for the isolation of large animals and for long-term care of small animals are required at the Rocky Mountain Laboratory. Temporary isolation facilities must be constructed. It is estimated that \$37,000 will be required to support three new positions and provide additional animals and equipment for this program.

Cooperative studies conducted by the Middle America Research Unit (Laboratory of Tropical Virology) and the Bolivia Health Ministry within the last few months indicate that Bolivian hemorrhagic fever (a disease apparently similar to Argentine hemorrhagic fever) is a virus infection of great importance not only to Bolivia but probably also to other areas of South America, including Colombia, Venezuela, Brazil, and the eastern slope of the Andes Range.

Over 500 cases with high mortality (a 20- to 30-percent fatality rate) have occurred in an isolated part of northeast Bolivia during the last 3 years. The disease may hinder the economic development of several fertile areas of South America.

Although the virus is presumably known, its mode of transmission and its source is not specifically known. It is presumed carried by arthropods from animal reservoirs. Studies on the epidemiology of the disease will require eight additional positions. Additional animal cages, isolation facilities, and other permanent equipment will be required. Because of the distance to Bolivia, there will be additional cost for travel of personnel and for the shipment of equipment. The estimated budget will be \$75,000 for 1964.

Preliminary results, announced in recent weeks, of trials in human volunteers of a new antimalarial, designated CI-501, have established the exceptional promise of this drug in offering long-lasting protection against the bites of heavily infected mosquitoes. In some experiments more than a year of protection has been demonstrated from a single injection of the drug, introduced by a pharmaceutical firm (Parke, Davis & Co.). Clinical trials in volunteers have been conducted on a limited basis through collaborative studies by the NIAID's Laboratory of Parasite Chemotherapy, a research group with many years of experience in testing antimalarials in clinics and under field conditions. Great interest has been expressed in pursuing research on CI-501 as rapidly as possible, because the findings to date represent one of the most dramatic demonstrations of progress against the world's No. 1 disease problem.

The Iranian Embassy, for example, has been in touch with NIAID malariologists concerning future plans. A group of missionaries on the way overseas wrote expressing willingness to participate in trials that must now be made under actual field conditions in malarious areas of the world. Broad U.S. participation in world malaria-eradication efforts may be greatly assisted if these trials are successful.

The Laboratory of Parasite Chemotherapy proposes to accelerate and extend the trials of CI-501, working through other U.S. Government agencies and the World Health Organization to set up sites for and to initiate field studies. The objective will be to determine rapidly whether the cost of malaria in human lives and economic disaster can be materially reduced by widespread use of CI-501. Comparing the probable initial cost of this venture with somewhat similar collaborative projects, a sum of \$300,000 should provide for establishing the undertaking during the first year.

Management fund, increase of \$796,000: This increase would provide additional support for the services furnished centrally by the National Institutes of Health management fund.

B. Collaborative studies, increase of 26 positions and \$3,763,000.—Vaccine development, increase of 20 positions and \$3 million: Extensive research efforts are currently being conducted to develop vaccines for the prevention of acute febrile respiratory illness and the common cold. Intensive efforts to find the causative agents of these illnesses have resulted in the identification of over 120 different viruses, some 50 of which have been implicated as causing the more common respiratory illnesses; of these, at least 15 are known to cause 60 percent of the acute febrile respiratory diseases in hospitalized children. While the goals of basic and epidemiologic research are being so satisfactorily approached, there remains a wide gap in the application of this knowledge in terms of the development of vaccines against respiratory disease than can be placed in the hands of practicing physicians. Indicative of the magnitude of this problem is the estimate by the National Foundation of the cost of developing the Salk polio vaccine at \$50 million. Consider the significance of this expenditure to provide a vaccine for control of only three virus strains, as compared to what will be required to provide vaccines for control of the many different viruses known to be responsible for respiratory illness. To begin to approach this seemingly formidable task, a modest program for respiratory vaccine development was begun during 1962 with a budget of \$400,000 concentrating on the intermediate

objectives of developing vaccines for control of acute febrile respiratory illness of the most vulnerable segments of the population—children, military, groups, and the aged. Contracts were awarded to commercial pharmaceutical firms for development of prototype vaccine products and to university and other medical centers to initiate studies of the incidence of illness in the specific population groups to be used for the assessment of the experimental vaccines. An increase of \$1.4 million for 1963 has enabled the Institute to award additional research and development contracts to the pharmaceutical industry and to establish several new vaccine evaluation centers. Some experimental vaccines have already been produced under this program, and are currently being tested by a vaccine evaluation center.

Institute scientists in the Laboratory of Infectious Diseases now provide a large measure of the laboratory and epidemiologic competence for technical direction of the vaccine development program. The program is, in part, dependent upon the scientific resources of the intramural research program for comprehensive technical liaison and collaboration with the contractors, and for continuous scientific review of contract projects. With the expansion of the vaccine development program, and as more experimental vaccines become available for testing, the involvement of the intramural scientists will increase; such an important program resource must be expanded to support this activity.

In order to sustain the growing momentum of this national research effort, and for the Institute to assume a realistic posture in providing the leadership for this effort, additional funds and personnel will be required during 1964. An increase of \$3 million and 20 positions is requested for the expansion of research contract programs and for adequate technical and staff support of the program activities.

Virus reagents, increase of six positions and \$763,000: Studies on the relationship of viruses to human disease comprise the fastest-moving area of research in microbiology today. New viruses are being isolated at a rapid rate, and hitherto undiscovered relationships between viral infections and human illness are being documented. Accurate identification of the viruses involved in these studies is a prime requisite to such research, yet the specific reagents (antigens and antisera) required for precise identification are generally not available in adequate quantities through commercial or other sources. As a consequence, investigators have been forced to devote a considerable portion of their energies and time to production and standardization of these essential tools in their own laboratories. The relative unavailability of reliable reagents thus led to an inefficient use of research time and a lack of uniform reagent preparations. As a result, identification of viruses and the resultant research reports frequently have not been comparable between laboratories.

The virus reagents program has been developed to meet this situation by providing to research workers a series of standardized reference reagents. Arrangements are in progress for endorsement of these preparations by the World Health Organization as international reference reagents. Thus a mechanism has been established to insure the comparability of virus identification by laboratories throughout the world.

Solid progress in the achievement of these goals has been made during 1963. Antigens and antisera will be available before the end of the year for 18 types of human adenoviruses. Similar reagents for about 20 more adenoviruses and approximately 20 other respiratory viruses, including the influenzas, parainfluenzas, and other immunologically related viruses, already are in production. Antisera for over 60 enterovirus types have been produced. Some of these are now ready for distribution, and packaging of the remainder is about to be undertaken. In the field of arthropod-borne viruses, preliminary studies have been carried out to evaluate possible methods for antiserum production, and plans are now being developed to initiate large-scale production of antisera for 11 virus types. A repository and distribution facility is now being established, with the expectation that availability of these reagents under a well-developed distribution policy will be announced to the scientific community about July 1963.

Technical advice in developing specifications for the production of reagents is provided by a number of advisory panels composed of outstanding research virologists. Through its Board for Virus Reference Reagents, the program is responsive to the requirements of all units of the National Institutes of Health in meeting their needs for viral reagents. The program operates chiefly through contracts with academic or commercial organizations capable of devoting adequate facilities and competent scientific staff to the production and testing of these highly competent biological products. All reagents are independently tested both by the producer and by a second laboratory selected by the program to certify the quality of the reagents. Heavy demands are made on the intramural staff of the Institute to provide the supporting laboratory services necessary to insure continued quality control through specialized testing, production of seed stocks, and other services. Continued success of the reagents program is dependent upon adequate funds for the support of these laboratory services.

Intensive research on the epidemiology of human respiratory illnesses and the possible relationship of viruses to human cancer is revealing a large number of hitherto unknown viruses. In order to meet the needs in this advancing frontier of research, the virus reagents program must move quickly into the production of reagents for these newly discovered viruses, particularly those within the recently established Picorna group. This work necessarily is developmental research which cannot follow preestablished patterns and protocols. Other areas demanding attention include studies on the shelf-life of reagents; improved production techniques and test procedures; and methods for the production of concentrated reagents to make possible numerous tests using small quantities of a patient's serum. As a corollary to the latter development, the program urges extensive production of working reagents (such as concentrated antigens) needed to implement the National Institutes of Health intramural and selected extramural investigations on the relationship of viruses to human disease.

An increase of six positions and \$763,000 would permit the program to broaden its service to microbiological research through production, testing, and distribution to research workers of reference and typing reagents not only for the new viruses which are being isolated at an accelerating rate, but also for selected bacterial agents such as the pneumococci, for which adequate reagents are not presently available. Moreover, increased funds would permit greater support of regional laboratories equipped to provide expert consultative service in the identification and study of viral isolates. The technical panels advisory to this program repeatedly have urged support of such laboratories to strengthen and coordinate research on the taxonomy and characterization of microbial agents.

Increasing concern for the problems of air pollution control make it imperative to intensify research on airborne allergens. A major stumbling block is the unavailability of standardized allergens with which to conduct research that can be properly compared to studies carried out in other laboratories. For nearly 4 years NIAID has been supporting a modest program of basic research on the "standardization of allergens. This activity now has reached the stage where a more aggressive approach is needed to procure large quantities of standardized allergens which can be made available to research allergists and immunologists.

4. Review and approval of grants, increase of nine positions and \$173,000

An increase of \$90,000 could be used effectively to strengthen the professional, managerial, and administrative capabilities of the extramural program. Increased professional staff is needed to provide assistance to the Allergy and Infectious Diseases Advisory Council, the Training Grants Committee, and the Fellowship Review Board in the programming of current research and training activities, and to encourage the exploration of areas of research which have been neglected in the past. Managerial staff increases would facilitate the comprehensive review of the business aspects of research and training grant applications and expenditure reports. It is expected that the Institute will have increased grants management responsibilities by 1964.

The difficulties in the administrative and clerical area result from increased workload in connection with the technical review and processing of research and training grant applications. This function has grown in volume and complexity without proportionate increases in staff. This is evidenced by the constantly increasing rate of overtime in this area.

Management fund.—An increase of \$83,000 will provide additional support for the services furnished centrally by the National Institutes of Health management fund.

5. *Program direction, increase of 11 positions and \$231,000*

Administration, increase of three positions and \$25,000.—The burden upon the administrative activity to provide services to the other activities of this Institute has increased in direct proportion to the expansion of the program responsibilities of each of the three major operating areas.

Program analysis, increase of eight positions and \$100,000.—The activities of program analysis and evaluation of NIAID requires a staff organization in order to support the analytical and planning operations of the Institute as well as policy formulation and administrative functions of the executive staff. Since the activities of program analysis require continued assessment and identification of programmatic problems and plans in all areas of the Institute, supporting staff of relevant competence will be necessary. Four major analytical branches are required; resources analysis, statistical analysis, management and fiscal analysis, a scientific and technical communications branch. These organizational functions will identify objectives within the categorical mission of the Institute, evaluate their priorities and anticipate in a comprehensive way their requirements for personnel, resources, and facilities. The general trends of national and international research in allergy and infectious disease will require continuing appraisal and the relationship of these trends to program development will be ascertained. The information analysis will be structured formally with recommending documents for advisory support to the Director of the Institute and for consideration of general policy consideration by the Advisory Council. The ramification of program decision, intramural, extramural and collaborative must be anticipated in a defined manner which will assist strategic planning by the Institute staff. Liaison will be established among the Institutes and other relevant private and Federal research agencies.

The manpower resources and need will be given particular attention in order to maintain the exponential growth of scientific research and to realize in a meaningful manner the impact of research programs upon educational institutions. Program analysis activities will also be responsible for the general supervision of new developments in scientific communication and will support the collation, compaction and integration of scientific information within the categorical mission of the Institute.

Management fund.—Increase of \$106,000. This increase would provide additional support for services furnished centrally by the National Institute of Health management fund.

NEUROLOGY AND BLINDNESS ACTIVITIES

Comparison of 1964 President's budget with 1964 professional judgment budget estimate

[In thousands]

	1964 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research.....	\$58,537	\$61,000	+\$2,463
Fellowships.....	2,054	2,500	+446
Training.....	14,382	15,000	+618
Total grants.....	74,973	78,500	+3,527
Direct operations:			
Research.....	7,193	7,293	+100
Collaborative studies.....	4,154	4,864	+710
Training activities.....	64	64	0
Review and approval of grants.....	1,664	1,759	+95
Program direction.....	359	399	+40
Total direct operations.....	13,434	14,379	+945
Total estimate.....	88,407	92,879	+4,472

1. Grants—Increase of \$3,527,000

A. Research grants—Increase of \$2,463,000

	1964 President's budget	1964 professional judgment budget	Increase
Continuations and supplementals.....	\$41,279,000	\$41,279,000	0
New grants.....	9,415,000	10,921,000	+\$1,506,000
Additional indirect costs.....	2,936,000	3,000,000	+64,000
Total regular programs.....	53,630,000	55,200,000	+1,570,000
General research support grants.....	3,662,000	3,755,000	+93,000
Scientific evaluation.....	45,000	45,000	0
Categorical clinical research centers.....	1,200,000	2,000,000	+800,000
Total research grants.....	58,537,000	61,000,000	+2,463,000

The funds for new grants provide for the normal growth of new approved applications plus approximately \$1 million for the program in drug evaluation.

The Institute increasingly is attempting to mobilize the efforts of groups of scientists for continual surveillance and direction of given fields, analysis of program needs, encouragement and development of research programs, and to serve as a medium for scientific communication.

Among such special groups is an Institute-sponsored committee on drug evaluation with separate panels on certain major disease categories. These panels have continued to develop improved techniques for evaluating drugs used to treat multiple sclerosis, Parkinsonism, headache, and neuromuscular disorders.

The development of each of these programs for evaluation of therapy requires the establishment of a central focus and coordination in data analysis. To serve adequately the national need, each such focus should include not only the conduct of field trials, but also responsibility for maintaining a complete over-view of the field, and an information center through which the profession can be rapidly advised regarding available drugs, their efficacy and the reported side effects.

An increase of \$800,000 is requested for the support of eight additional awards in the categorical clinical research center program.

By means of interdisciplinary approaches, it is anticipated that unique opportunities will present themselves to make significant advances in pathologic as well as physiologic processes of the nervous system. The intent is to bind the clinical and nonclinical research groups together by virtue of their common interest, training, and capacity in research on the nervous and sensory system; and to provide the opportunity for the translation of findings of patients and animal studies one to the other.

A future goal anticipated to be the development of regional multiinstitutional clinical research centers. At such centers, outstanding investigators from medical institutions in a geographic region area could utilize necessarily complex and highly expensive facilities which would not be feasible for the exclusive use of scientists in only one institution.

B. Fellowships, increase of \$446,000

	1964 President's budget	1964 professional judgment budget	Increase
Postdoctoral.....	\$804,000	\$804,000	0
Research career awards.....	1,250,000	1,696,000	+\$446,000
Total fellowships.....	2,054,000	2,500,000	+\$446,000

An increase of \$446,000 would support 17 additional individuals to develop further as independent scientists. This program is particularly important in the clinical research areas in that it provides an opportunity for the well-trained scientist-clinician to actively prepare for an academic career.

C. Training—Increase of \$618,000

	1964 President's budget	1964 professional judgment budget	Increase
Graduate training.....	\$10,670,000	\$11,288,000	+\$618,000
Undergraduate training.....	1,000,000	1,000,000	0
Traineeships.....	2,600,000	2,600,000	0
Scientific evaluation.....	112,000	112,000	0
Total training.....	14,382,000	15,000,000	+618,000

An increase of \$618,000 would support approximately 19 additional graduate training grants in the various fields of neurological and sensory disorders. Special emphasis will be given to additional training activities in selected disciplinary areas such as clinical research, neurochemistry, neuropathology, sensory physiology, acoustical physics, speech pathology, audiology, and public health.

2. *Direct operations, increase of \$945,000.*

A. *Research, increase of \$100,000.*—This amount of funds could be used in contracts with various companies who can furnish technical laboratory services, such as processing histopathological materials and chemical testing.

B. *Collaborative studies, increase of \$710,000.*—Office of Associate Director: An increase of \$33,000 will support six statistical and clerical positions required to support the current staff in conducting the increased activities of the Office of the Associate Director, Collaborative Research Branch.

Perinatal research: An increase of \$572,000 will provide support of 36 additional positions required for expansion of the current programs including obstetrics, pediatric neurology, statistical procedures and analyses, and virology. This increase will also provide for increased statistical processing costs. It is estimated that the data-processing requirements for 1964 will be over \$600,000. The President's budget includes \$190,000 for these costs.

Biometrics: An increase of \$25,000 would provide for additional contracts for studies such as: etiology of blindness due to prenatal factors; prenatal factors associated with strabismus in children, and deafness and other auditory diseases.

Special projects: An increase of \$80,000 would provide for the support of 11 additional positions required to initiate, organize, and direct or coordinate clinical trials related to the evaluation of therapy program.

C. *Review and approval, increase of \$95,000.*—Of this increase, \$45,000 would support five additional positions required for the Training Grants and Awards Branch, the Undergraduate Training program and the Grants Management program, initiated in 1963. An increase of \$50,000 could be used also for contract activities in assisting in the program analysis of NINDB training and research grant programs.

D. Program direction, increase of \$40,000.—This increase would support five additional positions required in the Office of the Director for the general administration, direction, and coordination of all institute programs, as well as the review of current and proposed operations and supervision and provision of administrative services on a centralized basis.

HISTORY OF CONGRESSIONAL ACTION ON BUDGET REQUESTS FOR NIH

Year	Budget request			Appropriation		
	Obligational cash	Liquidating cash	Contract authority	Obligational cash	Liquidating cash	Contract authority
1932.....	\$48,000			\$48,000		
1933.....	48,000			48,000		
1934.....	54,775			54,775		
1935.....	50,000			50,000		
1936.....	64,000			64,000		
1937.....	64,000			64,000		
1938.....	464,000			464,000		
1939.....	515,000			515,000		
1940.....	587,750			707,000		
1941.....	712,120			711,000		
1942.....	705,000			700,000		
1943.....	1,278,270			1,278,270		
1944.....	1,291,000			2,555,020		
1945.....	2,335,000			2,835,000		
1946.....	2,078,000			3,414,700		
1947.....	10,799,500			¹ 8,125,448		
1948.....	22,403,000			28,876,000		
1949.....	45,701,460		\$2,300,000	37,668,000		
1950.....	40,567,000	\$3,900,000	3,595,000	50,167,000	² \$4,925,000	\$10,300,000
1951.....	49,845,000	12,725,000		³ 47,334,750	12,725,000	
1952.....	53,386,000	5,648,000		52,477,291	5,198,000	
1953.....	55,005,000			59,030,750		
1954.....	56,340,000			71,153,000		
1955 ⁴	71,128,000			81,268,000		
1956 ⁵ ⁶	90,023,000			98,458,000		
1957 ⁵	⁷ 126,725,000			183,007,000		
1958.....	190,183,000			211,183,000		
1959.....	211,814,000			294,383,000		
1960.....	294,279,000			400,000,000		
1961.....	400,000,000			⁸ 560,000,000		
1962.....	583,000,000			⁹ 738,335,000		
1963.....	780,400,000			880,800,000		
1964.....	930,454,000					

¹ Includes \$386,500 transfers.

² Not less than \$3,000,000 was earmarked for liquidating cash; an additional \$1,175,000 was used for that purpose.

³ Excludes \$3,216,250 rescinded.

⁴ Excludes \$131,000 for Gorgas Memorial Laboratory.

⁵ Excludes \$147,000 for Gorgas Memorial Laboratory.

⁶ Includes \$90,000 transfer.

⁷ Includes \$200,000 transfer from other appropriations.

⁸ Includes \$12,139,000 for construction of mental health-neurology research facility.

⁹ Includes \$1,000,000 for planning for a gerontological research facility; and \$750,000 for modernization at the Rocky Mountain Laboratory, Hamilton, Montana.

NOTE.—Not all amounts in this table are comparable from year to year because of inconsistencies in the content of the appropriations. Prior to 1938, they exclude all salaries. Prior to 1943 they exclude all salaries other than those of employees of the National Cancer Institute. Prior to 1949 they exclude pay of regular corps officers. For 1948, 1949, and 1950 they include funds for support of narcotic hospitals at Fort Worth and Lexington, which were subsequently transferred.

APPROPRIATION HISTORY AND OBLIGATIONS, 1957-64

SUMMARY—NATIONAL INSTITUTES OF HEALTH

	PHS estimate to Depart- ment	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
Total, operating accounts:							
1957-----	\$134,755,900	\$128,528,000	\$126,672,000	\$135,672,000	\$183,154,000	\$183,154,000	\$169,801,000
1958-----	202,487,000	192,280,000	190,183,000	190,183,000	226,783,000	211,183,000	210,261,000
1959-----	² 229,424,000	212,931,000	211,814,000	219,383,000	320,577,000	294,383,000	285,315,000
1960-----	337,846,000	309,096,000	294,279,000	344,279,000	480,604,000	400,000,000	390,350,000
1961-----	446,832,800	410,073,800	400,000,000	455,000,000	664,000,000	560,000,000	³ 545,616,000
1962-----	666,154,000	641,000,000	583,000,000	641,000,000	835,670,000	738,335,000	667,048,000
1963-----	885,314,000	855,000,000	780,400,000	840,800,000	900,800,000	880,800,000	-----
1964-----	1,049,825,000	954,493,000	930,454,000	-----	-----	-----	-----

¹ In addition, \$580,000 was transferred from "Grants to States for public assistance."

² Subsequent to 1958 Senate allowance this amount was increased to \$234,971,000.

³ Includes \$12,139,000 transferred to "Construction of mental health-neurology research facility."

NOTE.—"Obligations," on all tables, include rental payments made to GSA by transfer.

GENERAL RESEARCH AND SERVICES

	PHS estimate to Depart- ment	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$11,944,000	\$11,942,400	\$11,922,000	\$11,922,000	\$12,122,000	\$12,122,000	\$12,001,000
1958-----	14,097,000	14,161,000	14,026,000	14,026,000	14,026,000	¹ 14,026,000	14,081,000
1959-----	26,220,000	17,774,000	17,766,000	17,742,000	32,552,000	28,974,000	28,957,000
1960-----	35,299,000	30,766,000	28,974,000	36,404,000	49,585,999	45,994,000	45,789,000
1961-----	52,711,100	47,266,100	47,260,000	52,660,000	104,405,000	83,900,000	83,572,000
1962-----	122,683,000	119,275,000	95,341,000	119,275,000	140,000,000	127,637,000	118,205,000
1963-----	161,851,000	150,300,000	147,826,000	155,826,000	161,826,000	159,826,000	-----
1964-----	211,901,000	179,366,000	164,674,000	-----	-----	-----	-----

¹ In addition, \$58,000 was transferred to this account from "Grants to States for public assistance."

BIOLOGICS STANDARDS

	PHS estimate to Depart- ment	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1964-----	\$4,838,000	\$4,838,000	\$4,787,000	-----	-----	-----	-----

NATIONAL CANCER INSTITUTE

	PHS estimate to Depart- ment	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$35,222,300	\$32,875,700	\$32,437,000	\$34,437,000	\$48,432,000	\$48,432,000	\$42,556,000
1958-----	51,608,000	47,314,000	46,902,000	46,902,000	58,543,000	56,402,000	55,454,000
1959-----	58,943,000	56,744,000	56,060,000	57,423,000	81,129,000	75,268,000	69,398,000
1960-----	81,864,000	80,232,000	75,218,000	83,308,000	110,203,000	91,257,000	85,030,000
1961-----	95,995,400	88,785,400	88,869,000	102,469,000	126,375,000	111,000,000	106,262,000
1962-----	129,519,000	125,672,000	117,167,000	125,672,000	160,000,000	142,836,000	118,117,000
1963-----	158,901,000	155,700,000	139,109,000	150,409,000	158,409,000	155,742,000	-----
1964-----	154,999,000	145,706,000	145,114,000	-----	-----	-----	-----

MENTAL HEALTH ACTIVITIES

	PHS estimate to Department	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$23,939,700	\$21,916,200	\$21,749,000	\$23,749,000	\$35,197,000	\$35,197,000	\$30,274,000
1958-----	39,946,000	36,988,000	35,217,000	35,217,000	43,994,000	39,217,000	39,241,000
1959-----	39,718,000	37,895,000	37,788,000	40,397,000	55,896,000	52,419,000	49,889,000
1960-----	58,998,000	53,966,000	52,384,000	60,409,000	79,986,000	68,090,000	67,543,000
1961-----	78,693,200	73,610,200	67,563,000	79,863,000	110,800,000	100,900,000	² 97,191,000
1962-----	95,279,000	92,182,000	88,324,000	92,182,000	125,570,000	108,876,000	108,051,000
1963-----	138,652,000	135,800,000	126,899,000	133,599,000	148,599,000	143,599,000	-----
1964-----	206,061,000	193,277,000	190,096,000	-----	-----	-----	-----

¹ In addition, \$114,000 was transferred to this account from "Grants to States for public assistance."

² Includes \$5,139,000 transferred to "Construction of mental health-neurology research facility."

NATIONAL HEART INSTITUTE

	PHS estimate to Department	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$22,978,500	\$22,863,900	\$22,106,000	\$25,106,000	\$33,396,000	\$33,396,000	\$32,392,000
1958-----	35,822,000	33,815,000	33,436,000	33,436,000	38,784,000	35,936,000	35,973,000
1959-----	² 34,683,000	34,924,000	34,820,000	36,212,000	49,529,000	45,613,000	45,468,000
1960-----	52,911,000	47,671,000	45,594,000	52,744,000	89,500,000	62,237,000	61,565,000
1961-----	69,798,700	65,047,700	63,162,000	71,762,000	125,166,000	86,900,000	86,239,000
1962-----	110,205,000	105,723,000	97,073,000	105,723,000	160,100,000	132,912,000	110,899,000
1963-----	155,712,000	148,000,000	126,898,000	143,398,000	149,398,000	147,398,000	-----
1964-----	149,185,000	136,300,000	133,624,000	-----	-----	-----	-----

¹ In addition, \$147,000 was transferred to this account from "Grants to States for public assistance."

² Subsequent to 1958 Senate allowance this amount was increased to \$37,139,000.

NATIONAL INSTITUTE OF DENTAL RESEARCH

	PHS estimate to Department	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$3,237,700	\$3,067,500	\$2,971,000	\$3,471,000	\$6,026,000	\$6,026,000	\$5,949,000
1958-----	6,635,000	6,532,000	6,430,000	6,430,000	6,430,000	¹ 6,430,000	6,466,000
1959-----	7,719,000	6,481,000	6,359,000	6,543,000	7,923,000	7,420,000	7,405,000
1960-----	9,907,000	7,715,000	7,420,000	9,725,000	10,164,000	10,019,000	9,968,000
1961-----	13,803,300	11,996,300	11,204,000	12,604,000	16,710,000	15,500,000	14,616,000
1962-----	15,265,000	14,681,000	13,933,000	14,681,000	20,000,000	17,340,000	15,108,000
1963-----	20,017,000	19,700,000	17,199,000	19,199,000	22,199,000	21,199,000	-----
1964-----	23,314,000	20,212,000	19,809,000	-----	-----	-----	-----

¹ In addition, \$50,000 was transferred to this account from "Grants to States for public assistance."

ARTHRITIS AND METABOLIC DISEASE ACTIVITIES

	PHS estimate to Department	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$13,517,900	\$13,481,600	\$13,345,000	\$13,845,000	\$15,885,000	\$15,885,000	\$15,850,000
1958-----	18,027,000	18,024,000	17,885,000	17,885,000	23,548,000	20,385,000	20,480,000
1959-----	² 20,319,000	20,579,000	20,668,000	21,092,000	34,798,000	31,215,000	31,126,000
1960-----	37,014,000	32,564,000	31,215,000	37,790,000	51,200,000	46,862,000	46,182,000
1961-----	52,949,900	47,519,900	47,541,000	52,841,000	70,760,000	61,200,000	58,608,000
1962-----	77,783,000	73,661,000	68,740,000	73,661,000	90,000,000	81,831,000	78,956,000
1963-----	103,761,000	101,560,000	91,921,000	98,721,000	105,721,000	103,388,000	-----
1964-----	124,579,000	115,759,000	114,717,000	-----	-----	-----	-----

¹ In addition, \$97,000 was transferred to this account from "Grants to States for public assistance."

² Subsequent to 1958 Senate allowance this amount was increased to \$21,929,000.

ALLERGY AND INFECTIOUS DISEASE ACTIVITIES

	PHS estimate to Department	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$10,994,200	\$10,081,900	\$9,946,000	\$8,946,000	\$13,446,000	\$13,446,000	\$13,418,000
1958-----	16,407,000	16,405,000	17,400,000	17,400,000	17,400,000	¹ 17,400,000	17,506,000
1959-----	21,044,000	17,663,000	17,593,000	17,997,000	26,500,000	24,071,000	24,039,000
1960-----	29,126,000	25,379,000	24,071,000	30,286,000	41,000,000	34,054,000	34,025,000
1961-----	38,477,100	35,462,100	34,739,000	38,439,000	48,234,000	44,000,000	43,780,000
1962-----	54,833,000	52,182,000	48,322,000	52,182,000	60,000,000	56,091,000	54,676,000
1963-----	64,262,000	64,155,000	59,342,000	62,142,000	68,142,000	66,142,000	-----
1964-----	79,569,000	69,765,000	69,226,000	-----	-----	-----	-----

¹ In addition, \$114,000 was transferred to this account from "Grants to States for public assistance."

NEUROLOGY AND BLINDNESS ACTIVITIES

	PHS estimate to Department	Depart- ment esti- mate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropri- ation	Obliga- tions
1957-----	\$12,921,600	\$12,298,800	\$12,196,000	\$14,196,000	\$18,650,000	\$18,650,000	\$17,361,000
1958-----	19,945,000	19,041,000	18,887,000	18,887,000	24,058,000	21,387,000	21,060,000
1959-----	¹ 20,778,000	20,871,000	20,760,000	21,977,000	32,250,000	29,403,000	29,033,000
1960-----	32,727,000	30,803,000	29,403,000	33,613,000	48,966,000	41,487,000	40,248,000
1961-----	44,404,100	40,386,100	39,662,000	44,362,000	61,550,000	56,600,000	² 55,348,000
1962-----	60,587,000	57,624,000	54,100,000	57,624,000	80,000,000	70,812,000	63,036,000
1963-----	82,158,000	79,785,000	71,206,000	77,506,000	86,506,000	83,506,000	-----
1964-----	95,379,000	89,270,000	88,407,000	-----	-----	-----	-----

¹ Subsequent to 1958 Senate allowance this amount was increased to \$22,259,000.

Includes \$7,000,000 transferred to "Construction of mental health-neurology research facility."

1964 PRESIDENT'S BUDGET BY INSTITUTE AND ACTIVITY

Obligations by activity	Management fund	GRS-NIH	Biologics standards	Cancer	Mental	Heart	Dental	Arthritis	Allergy	Neurology	Total
Grants:											
Research.....		\$106,529,000		\$65,253,000	\$50,755,000	\$97,183,000	\$0,833,000	\$82,513,000	\$40,628,000	\$58,537,000	\$541,231,000
Fellowships.....		15,277,000		3,188,000	8,534,000	6,399,000	1,257,000	4,019,000	3,088,000	2,084,000	46,786,000
Training.....		37,256,000		12,620,000	66,048,000	13,179,000	4,805,000	14,420,000	7,992,000	14,382,000	172,602,000
State control programs.....					10,950,000						10,950,000
Total, grants.....		159,062,000		82,961,000	166,287,000	118,761,000	15,895,000	100,952,000	51,678,000	74,973,000	770,569,000
Direct operations:											
Research:											
Direct operating funds.....				8,762,000	6,025,000	5,678,000	2,322,000	6,866,000	7,120,000	3,255,000	40,028,000
Reimbursements:											
Research supporting services.....	1 (\$9,827,000)			2,624,000	1,365,000	1,321,000	411,000	1,664,000	1,355,000	1,087,000	9,827,000
Clinical supporting services.....	(12,865,000)			3,376,000	1,991,000	2,410,000	193,000	1,580,000	1,408,000	1,917,000	12,865,000
Administrative management.....	2 (\$3,418,000)			2,479,000	1,237,000	1,199,000	274,000	1,197,000	1,098,000	934,000	8,418,000
Advertising for nonformula items.....	(517,000)										
Cafeteria.....	(400,000)										
Total, reimbursements.....	(32,027,000)			8,479,000	4,583,000	4,930,000	875,000	4,441,000	3,861,000	3,938,000	31,110,000
Total, research.....	(32,027,000)			17,241,000	10,608,000	10,608,000	3,200,000	11,307,000	10,981,000	7,193,000	71,138,000
Collaborative studies:											
International research.....				42,120,000	4,363,000	1,426,000		713,000	5,284,000	4,154,000	58,060,000
Biologics standards:		1,073,000									1,073,000
Direct operating funds.....											
Reimbursements.....	(832,000)										3,955,000
Total, biologics standards.....	(832,000)										832,000
Training activities:											
Professional and technical assistance.....		150,000			1,001,000	250,000				64,000	1,465,000
Review and approval:					3,998,000						3,998,000
Direct operating funds.....		2,279,000		898,000	2,164,000	1,007,000	363,000	624,000	483,000	746,000	8,564,000
Reimbursements.....	3 (6,607,000)	862,000		1,071,000	1,070,000	1,176,000	166,000	845,000	509,000	918,000	6,607,000
Total, review and approval.....	(6,607,000)	3,131,000		1,969,000	3,234,000	2,183,000	529,000	1,469,000	992,000	1,664,000	15,171,000
Program direction:											
Direct operating funds.....		1,196,000		482,000	375,000	237,000	151,000	167,000	157,000	269,000	3,034,000
Reimbursements.....	(1,159,000)	62,000		341,000	230,000	159,000	34,000	109,000	134,000	90,000	1,159,000
Total, program direction.....	(1,159,000)	1,258,000		823,000	605,000	396,000	185,000	276,000	291,000	359,000	4,193,000
Cancer research facility.....				50,000							50,000
Heart Gerontology Building.....						435,000					435,000

ANALYSIS OF RESEARCH GRANTS REQUIREMENTS

1964 requirements

[In thousands]

	GRS-NIH	Cancer	Mental	Heart	Dental	Arthritis	Allergy	Neurology	Total
1. Continuations:									
(a) Noncompeting	\$33,299	\$34,583	\$29,919	\$51,351	\$4,711	\$46,973	\$20,270	\$28,196	\$249,302
(b) Competing	5,216	7,964	9,884	10,668	838	8,104	9,150	11,571	63,395
2. Supplementals	2,465	2,989	1,822	6,251	238	3,200	2,000	1,512	20,477
3. Subtotal, continuations and supplementals	40,980	45,536	41,625	68,270	5,787	58,277	31,420	41,279	333,174
4. New grants:									
(a) Carryover									3,000
(b) Wholly new	20,920	15,501	29,935	18,634	3,142	16,480	3,000	10,921	127,033
5. Additional indirect costs:									
(a) At 20 percent ¹	2,691	2,654	3,111	3,779	388	3,250	1,996	2,269	20,138
(b) At 25 percent ²	898	885	1,038	1,200	129	1,083	666	757	6,716
6. Subtotal, regular program	65,489	64,576	75,709	91,943	9,446	79,090	48,582	55,226	490,061
7. General research support grants	4,026	3,849	4,042	6,107	605	5,193	2,516	3,662	30,000
8. Scientific evaluation grants	938	146	161	25	15	20		45	1,350
9. International centers for medical research and training	3,000								3,000
10. Gorgas Memorial Laboratory							250		250
11. Clinical research centers:									
(a) General	27,900								27,900
(b) Categorical		4,900	1,750	1,600	350	1,250	1,000	1,200	12,050
12. Special resource centers	6,000								6,000
13. Primate centers	5,700								5,700
14. Total, research	113,053	73,471	81,662	99,675	10,416	85,553	52,348	60,133	576,311

¹ Relates to all grants approved for 1964 support.² Relates to proposed increase in indirect cost rate to 25 percent for grants awarded on or after Jan. 1, 1964.

FRIDAY, MARCH 8, 1963.

GENERAL RESEARCH AND SERVICES

WITNESSES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. CLINTON C. POWELL, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

DR. FREDERICK L. STONE, CHIEF, DIVISION OF RESEARCH FACILITIES AND RESOURCES

DR. MARTIN M. CUMMINGS, CHIEF, OFFICE OF INTERNATIONAL RESEARCH

RICHARD L. SEGGER, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	937	1,768	2,507
Positions other than permanent.....	60	81	99
Other personnel compensation.....	27	28	112
Total personnel compensation.....	1,024	1,877	2,718
12 Personnel benefits.....	87	171	254
21 Travel and transportation of persons.....	169	340	693
22 Transportation of things.....	4	54	76
23 Rent, communications, and utilities.....	42	89	182
24 Printing and reproduction.....	18	67	75
25 Other services.....	279	402	456
Payment to National Institutes of Health management fund.....	681	891	931
26 Supplies and materials.....	31	85	116
31 Equipment.....	71	66	113
41 Grants, subsidies, and contributions.....	117,512	150,522	159,062
Subtotal.....	119,918	154,564	164,676
Deduct quarters and subsistence charges.....			2
Total obligations.....	119,918	154,564	164,674

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	188	315	394
Full-time equivalent of other positions.....	8	12	15
Average number of all employees.....	148	259	348
Number of employees at end of year.....	178	297	379
Average GS grade.....	7.1	7.5	7.5
Average GS salary.....	\$7,196	\$6,964	\$7,058

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	78,004	102,682	106,529
(b) Fellowships.....	10,593	14,164	15,277
(c) Training.....	28,915	33,676	37,256
Total, grants.....	117,512	150,522	159,062
2. Direct operations:			
(a) International research.....			1,056
(b) Training activities.....		150	150
(c) Review and approval of grants.....	1,870	2,740	3,131
(d) Program direction.....	481	1,152	1,275
Total, direct operations.....	2,351	4,042	5,612
Total program costs, funded ¹	119,863	154,564	164,674
Change in selected resources ²	55		
Total obligations.....	119,918	154,564	164,674
Financing:			
Comparative transfers to or from (—) other accounts.....	—1,761	4,845	
Unobligated balance lapsing.....	9,432	332	
New obligational authority.....	127,589	159,741	164,674
New obligational authority:			
Appropriation.....	127,637	159,826	164,674
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (—).....	—48	—85	
Appropriation (adjusted).....	127,589	159,741	164,674

¹ Includes capital outlay as follows: 1962, \$32,000; 1963, \$66,000; 1964, \$113,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$404,000 (1962 adjustments, \$180,000); 1962, \$639,000; 1963, \$639,000; 1964, \$639,000.

Mr. FOGARTY. All right, Doctor. We will now take up "General research and services."

GENERAL STATEMENT

Dr. SHANNON. Mr. Chairman and members of the committee, this appropriation provides funds for the support of general, noncategorical operating programs of the National Institutes of Health. The 1964 request totals \$164,674,000 compared to the 1963 operating level of \$154,564,000 or an increase of \$10,110,000.

There are some major differences in the composition of the programs included in the 1964 appropriation request from the budgets presented in previous years. The more significant changes are the removal of the budget for the Division of Biologics Standards which, in accordance with the wishes of this committee, is being presented as a separate appropriation, and the addition of the estimates for the Office of International Research, which were formerly presented as a part of my immediate office.

ORGANIZATION OF INSTITUTE

Mr. Chairman, the 1964 request includes funds for programs administered by three separate organizations—and I might say in your budget summary group, there is a breakdown of dollars by activity of each of these activities.

The page of that is page 4.

Mr. FOGARTY. Yes.

Dr. SHANNON. These three separate organizations are the National Institute of General Medical Sciences, the Division of Research Facilities and Resources, and the Office of International Research. The budget you have before you has been developed in accordance with the standard budget activity pattern, but I believe it would be most helpful to the committee if I discussed this request in relation to the programs of each of the three organizational components just mentioned. For the convenience of the committee, therefore, we have prepared a table which summarizes the relationship of the estimates for these three organizations to the standard budget activity structure. This table is on page 4 of the justifications, as I mentioned a moment ago.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

I will first discuss the request of the National Institute of General Medical Sciences, but first, Mr. Chairman, may I introduce Dr. Powell, who heads the National Institute. Dr. Clinton Powell came to us from a long experience in the Division of Research Grants, and was in charge of the grants program in the National Institute of Allergy and Infectious Diseases, and replaced Dr. Halsey Hunt, as Chief of the Division of General Medical Sciences which, in accordance with congressional action, has now become an Institute.

Dr. Powell is the gentleman to my left.

The National Institute of General Medical Sciences then, should be discussed first.

The amount of \$118,332,000 is requested for the National Institute of General Medical Sciences. This is an increase of \$14,511,000 over the 1963 level for this Institute.

The National Institute of General Medical Sciences administers the NIH grant programs for research in the sciences basic to medicine and biology, to public health, and to certain clinical sciences and multi-categorical programs not covered by other institutes or divisions. In addition, the Institute administers the grant programs for training investigators in the basic biomedical sciences and provides fellowships for general research training.

RESEARCH COVERAGE OF INSTITUTE

The research coverage of the Institute is broad. Included in its programs are the natural and behavioral sciences, such as anatomy, biochemistry, biomathematics, biophysics, molecular biology, cellular biology, enzymology, epidemiology, genetics, microbiology, pharmacology, cultural and comparative anthropology, and sociology. Certain clinical sciences are also included, such as general surgery, orthopedic surgery, dermatology, pathology, and anesthesiology, as well as various methodologies of science, including electronmicroscopy and biostatistics and the like. Such research is essentially noncategorical. Knowledge gained from it nourishes all of the life sciences. And I might add, not contained in the written summary, that the basic work of this Division has general relevance to most categorical missions of our other national Institutes.

Today, this area of research constitutes one of our largest extramural operations. Its importance has further been recognized by its recent elevation to institute status by act of Congress.

TRAINING PROGRAMS

To help supply the trained scientists required for the increasingly complex medical research of the future, the National Institute of General Medical Sciences operates graduate training programs in 15 areas. The budget provides for expanding these programs in the year ahead. Special emphasis is being placed on the fields of developmental biology, biomedical engineering, and the basic behavioral sciences, where training needs are the most urgent.

Supplementing the training grant activity is the Institute's fellowship program which supports the training of competent investigators and provides career opportunities for scientists of superior potential and capability. This program is also being expanded in the coming year.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

I will next turn to the Division of Research Facilities and Resources.

This Division is under the direction of Dr. Frederick L. Stone, who is seated next to Dr. Powell. Dr. Stone accepted responsibility for the administration of this Division at its inception. Dr. Stone, too, has had a rich experience in the administration of research grants. He was Dr. Halsey Hunt's Associate Director in the Division of General Medical Sciences, and moved in as Chief of the new Division of Research Facilities and Resources when it was established last summer.

This Division provides support for facilities and resources to meet the broad health-related research needs of institutions or groups of institutions. The 1964 budget requests \$40,919,000 for the Division's program for general clinical research centers, special resource centers, and primate centers. The Division also administers the health research facilities program which is presented in a separate appropriation. This program, as you know, amounts in authorization to \$50 million. The Division also administers the general research support grants program which is supported through funds transferred from research grant moneys of all the operating appropriations.

RESEARCH CENTERS

The general clinical research centers program is solidly embarked upon a multidisciplinary effort to improve and expand the national level of clinical research in human diseases, and to seek out new knowledge concerning human metabolism. Thirty-six centers are now operating throughout the Nation and 24 others are in various stages of preparation. They provide a stable organizational framework; an atmosphere of common purpose linking research, teaching, and treatment; and they offer a stimulating intellectual environment for research of high quality.

Special resource centers are operated to provide specialized or unusual research services to institutions or groups of institutions. Eighteen have been established thus far, 17 for computer operations and 1

in biomedical engineering. As more scientists become capable of utilizing these powerful new tools the demand for computer utilization in research can be expected to increase rapidly. Other types of special resource centers under discussion are biomedical engineering and instrumentation centers; centers for the production of pure lines of mammalian cells in large quantities, and centers for the large-scale production of enzymes, selected proteins, and special subcellular components. These necessary biological materials, which some of the advanced sciences are supporting today, are quite beyond the capabilities of being produced within the individual research project. They, in a sense, provide research services for different projects supported throughout the country. Without any doubt, this approach to aiding groups of institutions to advance or improve their research capability will contribute powerfully to a combined, multicategorical attack on the diseases of man.

REGIONAL PRIMATE CENTERS

The regional primate centers program has added three new primate projects this past year, to its original four. Thus it has a much better regional coverage in areas of high demand. Of the seven, two are in the Northwest, one in the Southwest, one in the Midwest, one in the East, and two in the South. In their work with subhuman primates, scientists are discovering an increasing number of physiological and biochemical similarities to humans, thus enabling man to gain new knowledge with which to exercise increasing control over his own health and well-being. In addition to the regional designation given above, an identification of the specific institution will emphasize further geographic dispersion: The Medical Research Foundation of Oregon affiliated with the University of Oregon at Portland, the University of Wisconsin at Madison, the University of Washington at Seattle, Harvard University at Cambridge, Tulane University at New Orleans, Emory University at Atlanta, and the University of California at Davis.

GENERAL RESEARCH SUPPORT GRANTS

The general research support grants program allows institutions to meet emerging opportunities in research, to explore new and unorthodox scientific ideas, and to use research funds in ways that will contribute to long-range institutional development for improved research achievements. During fiscal year 1962, 153 general research support grants totaling \$20 million were made to schools of medicine, dentistry, osteopathy, and public health in 26 States, the District of Columbia, and Puerto Rico. In 1963 the program was increased to \$30 million, which will, in addition to providing general research support for those schools previously eligible, give support to approximately 100 research organizations, schools of pharmacy, and veterinary medicine, in dependent teaching hospitals and other nonprofit research organizations substantially involved in health-related research and research training. In all there will be about 300 institutions receiving this kind of support by the end of 1963.

A much needed extension of the general research support grant program has been under study for some time. This extension, if implemented, anticipates the accelerated, advanced development of a few model centers for health research and research training. Medicine and society will both be enriched by bringing the health sciences into closer working relations with the mainstream of university research and scholarly activities. Medicine stands in need of a higher level of coordination with fundamental research in the biological and physical disciplines, engineering, and the social and behavioral sciences.

The interdependence of hitherto disparate elements of the university has now become abundantly evident. This is especially clear in relation to the most powerful central problems medicine is facing—problems of understanding the living processes that control heredity, reproduction, cellular organization and proliferation, the hierarchy of integrative systems, individual biological development, and behavior.

During the coming year we will start a systematic inquiry to determine whether the time is right for establishing a few models across the country for research and research training in settings where excellence in advancing techniques and concepts can be most effectively brought to bear on health-related research problems and where the convergence of hitherto isolated disciplines can be purposefully accelerated.

INTERNATIONAL ACTIVITIES

Turning to the international activities, under the leadership of Dr. Martin Cummings, who is the gentleman at the table to my left.

I might say, in introducing Dr. Cummings, he has a very rich experience in both the building and administering of research; he comes to us from the University of Oklahoma, but prior to coming to us, he had major responsibility for the research programs at the Veterans' Administration; he returned to the university about 3 years ago, to head the department of microbiology, and we felt it would be wise to encourage his return to the Federal establishment, and he returned as head of the Office of International Research. We are very deeply impressed by the program which he developed and glad to say that he finds the opportunity a challenging one.

Under his leadership, the Office of International Research provides a focal point within NIH for policy formulation and guidance and coordination for all NIH international activities. This Office is also responsible for the administration of a number of programs, among which are the international centers for medical research and training, international postdoctoral fellowships, the international research associate program, and the special foreign currency program. In addition, this Office administers the NIH oversea offices which are engaged in developing and gathering information related to our foreign activities. The estimates for these programs are contained in this appropriation, with the exception of the special foreign currency program which is presented in a separate appropriation.

Dr. Cummings is prepared to give you further details on this and our other international activities in response to any questions you may have.

Mr. Chairman, this is a brief summary of the activities in this appropriation, and I believe Drs. Powell, Stone, and Cummings are prepared to elaborate on any of these in response to your questions.

Mr. FOGARTY. Thank you, Doctor.

PREPARED STATEMENT

Dr. SHANNON. Before the questions, sir, I omitted to say that I just read a brief summary and if I may, I would like to submit a more definitive statement for the record.

Mr. FOGARTY. All right. Put that in the record.

Dr. SHANNON. Yes, sir.

(The statement follows:)

Mr. Chairman and members of the committee, this appropriation provides funds for the support of general, noncategorical operating programs of the National Institutes of Health. The 1964 request totals \$164,674,000 compared to the 1963 operating level of \$154,564,000, or an increase of \$10,110,000.

There are some major differences in the composition of the programs included in the 1964 appropriation request from the budgets presented in previous years. The more significant changes are the removal of the budget for the Division of Biologics Standards which, in accordance with the wishes of this committee, is being presented as a separate appropriation and the addition of the estimates for the Office of International Research which was formerly presented as a part of my immediate office.

Mr. Chairman, the 1964 request includes funds for programs administered by three separate organizations—the National Institute of General Medical Sciences, the Division of Research Facilities and Resources, and Office of International Research. The budget you have before you has been developed in accordance with the standard budget activity pattern, but I believe it would be most helpful to the committee if I discussed this request in relation to the programs of each of the three organizational components just mentioned. For the convenience of the committee, therefore, we have prepared a table which summarizes the relationship of the estimates for these three organizations to the standard budget activity structure.

I will first discuss the request for the National Institute of General Medical Sciences.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

This Institute administers the NIH grant programs for research in the sciences basic to medicine and biology, to public health, and to certain clinical sciences and multicategorical programs not covered by other institutes or divisions. In addition, the Institute administers the grant programs for training investigators in the basic, biomedical sciences and provides fellowships for general research training. These programs are essentially noncategorical. Knowledge gained from them nourishes all of the life sciences and serves to undergird the categorical programs which are primarily disease oriented.

The research coverage of the Institute is broad. Included in its programs are the natural and behavioral sciences, such as anatomy, biochemistry, biomathematics, biophysics, molecular biology, cellular biology, enzymology, epidemiology, genetics, microbiology, pharmacology, cultural and comparative anthropology, and sociology. Certain clinical sciences are also included, such as general surgery, orthopedic surgery, dermatology, pathology, and anesthesiology, as well as various methods of science, including electromicroscopy and biostatistics.

Research grant activities

Numbered among the grantees of the National Institute of General Medical Sciences are many of the Nation's outstanding investigators. Their achievements in the past year have been unusually noteworthy, and the honors accorded certain of them include the highest awards in science and medicine.

James Dewey Watson, of Harvard University, an NIH grantee since 1957, became at 34 years of age one of the youngest men ever to win a Nobel prize. In association with the British scientist, Francis H. C. Crick, he elucidated the helical structure of deoxyribonucleic acid (DNA). This molecule holds

the key to the "genetic code," which furnishes instructions for the production of proteins and genetic material. The study of heredity, cancer, viral disease, mental disease, and a host of disorders designated as "inborn errors of metabolism" will be advanced by this fundamental achievement.

Dr. Choh Hao Li, of the University of California at Berkeley, a long-term grantee of NIH, was a recent recipient of the coveted Lasker Award for medical research. Dr. Li first isolated and identified the adrenocorticotrophic hormone (ACTH) and five other hormones of the anterior pituitary gland. He also synthesized a smaller molecule, containing about one-half the natural hormone's amino acids and having approximately half as much activity in stimulating the adrenal gland. He later synthesized a smaller fraction, which shows only slight adrenal-stimulating activity but promotes the breakdown of certain types of fats in the body. As a result of these studies, new knowledge of metabolic disease, allergy, immunity, inflammatory disease, arthritis, and other diseases will be enhanced.

Nobel Laureate Albert Szent-Györgyi, whose work has been supported by NIH since 1948, recently announced some significant discoveries concerning the thymus gland. After 10 years of work, he and his associates at the Institute for Muscle Research, Woods Hole, Mass., succeeded in isolating two powerful chemical substances from the thymus gland of calves. One of these is a potent promoter of growth, and the other an equally potent growth inhibitor. These properties were exhibited also in experimental cancer in mice. More recent studies by the same investigators suggest that the growth-stimulating factor, promine, actually consists of two substances, a growth promoter, and a juvenility or sterilizing fraction. These investigations have broad implications.

The research activities supported by the National Institute of General Medical Sciences are concerned with the understanding both of normal biology and of disease processes. In a direct sense, they furnish reserves of knowledge fundamental to the programs of other institutes which support the applied or categorical sciences and, in particular, the clinical sciences.

Not too long ago, it was considered that the range of investigational interest in the life sciences extended only down to the cellular or subcellular level. Today, it is recognized that biology must concern itself not only with molecular relationships, but also with submolecular phenomena. It is becoming apparent that each part of a molecule of protein or of a nucleic acid has a special significance in terms of specific activity and function. We are moving into new dimensions in the study of submolecular structure and of the relationships of chemical processes to health and disease. A beginning has been made in the recognition of specific molecular diseases such as cystic fibrosis, galactosemia, histidinemia, and Wilson's disease.

Underlying the approach to such complex and poorly understood diseases is basic research in genetics. It is here that investigators seek an understanding of the total metabolic process and how it relates to the ultimate control of many disorders of development and of other life processes. For the highly trained scientists who are charting the biochemistry and biophysics of genetics, this field is the most challenging frontier in the biological sciences.

Research training activities

The training programs of the National Institute of General Medical Sciences have as their central mission the support of research training and teaching in the fundamental health sciences. Like the Institute's research grants program, this activity serves as a base for categorical programs and thus is an indispensable source of strength to all of the institutes at NIH.

Support for the training of scientific manpower for future research and teaching requires a variety of award systems tailored to fit the special needs of institutions and individuals.

Through its regular graduate training programs, the Institute is supporting training in 15 areas: Anatomical sciences, anesthesiology, behavioral sciences, biomedical engineering, biochemistry, biometry, biophysical sciences, developmental biology, epidemiology, genetics, microbiology, nutrition, pathology, pharmacology, and physiology. Each of these programs functions under the guidance of a training committee composed of non-Federal scientists and other experts in the particular field in question.

Complementing the training support in these specific graduate disciplines are two other programs of a very broad nature: Medical student research training grants and the medical scientist program.

During the past few years, upon the recommendations of the National Advisory Health Council and other expert consultants, increased emphasis has been placed on support for training in certain special fields which are becoming important to health-related research. Several of these merit comment here.

Research and training for research in the basic behavioral sciences is a matter of growing importance and, indeed, urgency. Training in this area will supplement the programs of the National Institute of Mental Health, which are of a specifically disease-related nature. The initial goal has been the establishment of training programs in social anthropology, and in basic elements of the learning process.

There is a similar need for stimulation of the basic developmental sciences because of their multidisciplinary nature. Much of the research deals with embryology and the mechanisms involved in the differentiation of primitive cells into specialized cells and tissue systems, cellular physiology, and immunochemistry and pharmacology as they affect fetal structure and functions. These sciences are likewise of significant interest to all the categorical programs, including the National Institute of Child Health and Human Development. As this program develops, some elements of it may be transferred to the latter Institute at a future date.

Another field greatly in need of support is biomedical engineering, which is concerned with the development and application of measurement and control systems in connection with biological investigations and medical procedures. While it has been inevitable that biology and medicine should form a partnership with engineering, there have been practical difficulties in achieving this welding of interests in the training of individuals. In the years ahead, biologists, physicists, chemists, engineers, and mathematicians will be expected to take advantage of the increasing availability of new instrumentation.

With funds first provided in the 1961 budget, the Institute has extended its program embracing research career development awards, which are made to young investigators seeking advanced opportunities for research, and research career awards, which go to established investigators already in productive careers of independent research and teaching but without adequate current support.

Program analysis

Accompanying the growth of the Institute's programs, it has become necessary to provide adequate machinery by means of which proposed and existing activities may be subject to continuous review. To implement this, the Institute has established a Program Analysis Branch which is charged with responsibility for planning, consultation, data accumulation and evaluation of the various programs of the Institute. Guidance provided by this Branch will enhance our prospects of adding materially to the Nation's storehouse of knowledge in the basic medical sciences.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

The principal task of this Division is to bring together under one unit a group of active extramural programs featuring broad institutional or regional support for research in the health-related sciences.

Five basic programs constitute the principal Division objectives—construction of new or remodeled biomedical research facilities (for which there is a separate budget request), establishment of general clinical research centers, support for computer and other special resources wherever there are sizable research programs capable of employing them profitably, the provision of subhuman primates for medical research, and the general research support program (financed as a percentage of all NIH research grants). The Division is charged with assisting in the advancement of medical knowledge through research over the broadest possible spectrum.

The NIH general clinical research centers program was started in the fall of 1959 following recommendations by the Congress in connection with the fiscal year 1960 appropriations act. Prior to establishment it was observed that not only could the quality of research as applied to patients be greatly enhanced by Federal assistance, but clinical accomplishments stemming from sound laboratory research could be put to use much more rapidly.

Specifically, the principal objective of this national program is to improve the quality and expand the scope of clinical research by the provision of an adequate base for human observation both in health and in serious disease. A costly endeavor, indeed, but one without which broadly supported laboratory

research in the health fields is pointless. As of January 1, 1963, 58 institutions in 26 States, the District of Columbia, and Puerto Rico, have received assistance for 60 general clinical research centers with a planned total of 739 beds. Of these 60 centers, 36 are now in operation; each is a discrete unit and provides the essential though complex integration of resources which permit penetrating and significant observations of a quantitative nature upon the human subject.

The profound impact of this relatively new national program can be judged by two different but interrelated measures: Specific research findings and the effect upon clinical research activity in the grantee institutions. Some idea of the variety and scope of research findings to be expected can be gained from the following samples that have been selected from a long list of scores of published results:

Muscular dystrophy has been linked to disturbances in metabolism by high-energy phosphates. Special compounds of nucleic acid may be of therapeutic value.

Use of a transistorized "pacemaker" for stimulating the heart with radio waves has proven to be practical on seven patients with heartblock. (Using the same method to study heart output at varying radio-controlled heart rates, allows determination of the optimal heart rate for each patient.)

Certain lung cancers have been found to secrete a polypeptide which stimulates production of large quantities of adrenal cortical steroids leading to severe Cushing's syndrome (a condition characterized by obesity, muscle wasting, skin atrophy, salt and water retention, etc.)

Use of the artificial kidney has proven its ability not only to save lives but to maintain the health of selected patients for as long as 2 years.

A method of determining the lifespan of human blood platelets was developed and applied to studies of blood banking methods and diseases associated with abnormal bleeding.

It has been demonstrated that the anemia and hemolytic tendency of most patients with paroxysmal nocturnal hemoglobinuria (the periodic nightly appearance of red blood cells in the urine) can be corrected with iron and anabolic steroids.

Scientific papers resulting from research accomplishments at these centers are continuing in a steady flow.

Fully as significant as the individual research findings themselves is the startling effect upon large sections of clinical research in the various recipient institutions. One institution has reported that during the last complete year of its clinical center operation some 30 new clinical research projects were conducted, of which about 25 would not have been started without the facilities provided. Equally as important was the institution's conviction that the level of additional clinical research undertaken was enhanced significantly by the excellent clinical center and staff thus made available.

It is anticipated that over and above funds spent this year to maintain general clinical centers already in existence, and to bring others into full research status, there will be grants for establishing about six new ones. Currently under review, for example, is an application for a new type of general clinical research center, namely, a maternal child center. There are indications that other institutions are planning similar units, especially those with considerable research activity relating to studies of pregnancy and newborn children. The question as to where these particular types of general clinical centers now should be placed for administration and program responsibility is under study.

The special research resources program is designed to provide specialized research capability, including equipment and manpower, which will markedly increase or enhance the research productivity of an institution or a region. A basic requirement of this program is that funds be granted only for resources that are used by many scientists working on an interdisciplinary basis either in one or in many institutions within a region. In some instances, a special resource may serve scientists throughout the Nation.

This program is now contributing to the support of 17 computer centers where vast amounts of data are processed in an incredibly short time, thus reducing the lag between basic discoveries and their possible application to physical and mental diseases. While these computers now serve a useful purpose in certain aspects of biomedical research, a second phase of the program anticipates the development of computer technology designed especially for biomedical research—useful for investigations in more sophisticated experiments. This type of advanced computer development is not now being satisfied by industry or by

university centers. An important step toward this goal was taken recently in a cooperative arrangement between the NIH and NASA with the Massachusetts Institute of Technology. There a "center development office for computer technology in the biomedical sciences" has been set up, supported in part by the special research resources program.

Another established center has demonstrated admirably the effectiveness of the computer in research projects of the university medical center where it is located, and has assisted also in research projects of several other institutions with whom cooperative arrangements were made. Among these are State mental hospitals, Veterans' Administration hospitals, public health departments, a number of medical schools, and voluntary health agencies. Studies for which the center has been used include the monitoring of fetal heart sounds, factor analyses of surgical risks, air pollution, blood pressure and tranquilizers, the analysis of electroencephalographic records, correlation of ketosteroids to obesity, and the relation of therapy methods to types of cancer.

As more scientists develop the competence to use computers as a resource for speeding research on problems once considered either too difficult or insoluble, the demand for computer centers is expected to increase rapidly. Reviewed at the November 1962 National Advisory Health Council meeting were 15 new applications; 13 for computers, 1 in biomedical engineering, and 1 in the biomedical information field. Five were approved and one was deferred pending a future site visit.

Although program emphasis has thus far been preponderantly oriented toward developments in computer technology and computer usage for health-oriented research, it is expected that an increasing number of applications will feature other types of centers. These too, will be designed to aid institutions or regions totally, so that they can advance or improve their research capability and thus contribute powerfully to a combined multicategorical attack on the dread diseases.

A special research resource in biomedical engineering, recently established at Northwestern University, for example, promises to establish a healthy academic climate where electronic, chemical, mechanical and other engineers can work with biomedical scientists to develop new concepts and instruments for advancing the study of human physiology; developing, for example, new methods of monitoring bodily functions. This is one of the centers now being supported by the special resource centers program.

A successful example of special research resources is the regional primate research centers program which was started in 1960, "to advance research in cardiology" following advice from the National Advisory Heart Council. It soon became apparent that the need for using primates in research was great in a much broader scope such as infectious diseases, reproductive physiology, cancer, arthritis, aging phenomena, etc. Consequently, these centers will now be a resource for all areas of biomedical research. Awards have been made for seven primate centers, three in the West at Beaverton, Oreg., Seattle, Wash., and Davis, Calif.; and four in the East at Madison, Wis., Boston, Mass., Atlanta, Ga., and New Orleans, La.; each to serve biomedical research institutions in its respective area.

Such primate research centers will provide facilities especially designed to house certain species of primates and will include research laboratories where a resident staff as well as visiting scientists representing many disciplines can conduct research. It is expected that new facts will be learned concerning the biological characteristics of both healthy and diseased primates throughout their entire lifespan. In primates, scientists are discovering an increasing number of physiological and biochemical similarities to humans, thus enabling man to gain new knowledge with which to exercise increasing control over his own health and well-being. Centers already underway promise to add appreciably to the Nation's total research potential.

Other types of special research resources presently being discussed with institutions include centers for the production of large quantities for pure lines of mammalian cells and centers for the large-scale production of enzymes, selected proteins, and certain subcellular components. These two types of centers when established will markedly increase the research productivity of scores of scientists who otherwise can get but slight quantities of the needed materials, often not of the appropriate cell line or of the desirable purity in the latter case where enzymic studies are involved.

The general research support program provides grants to schools of medicine, dentistry, osteopathy, public health, pharmacy, nursing, veterinary medicine, hospitals, and other nonprofit research organizations heavily engaged in health-related research. Each eligible educational institution receives a basic amount to insure that it will have a minimum financial base for a research and research training program. The total grant is computed according to a formula whose factors depend in large measure upon the total health-related research expenditure of the recipient institution in its latest complete fiscal year; the amount of its Federal and non-Federal grants, contracts, or gifts received; and finally, on available Federal funds.

General research support grants are distributed on the basis of professional evaluations of the unique capabilities and needs of the various institutions. They are not made to finance any specific projects or programs but may be used by grantee institutions to give added strength to their medical research and research training programs in ways the institutions judge to be most effective—subject, of course, to general guidelines and policies affecting all Public Health Service grants.

A much needed extension of the general research support grant program has been under study for some time. This extension, if implemented, anticipates the accelerated, advanced development of a few model centers for health research and research training. Medicine does not stand alone; it constitutes a significant and interdependent part of man's total intellectual enterprise. As a body of scientific disciplines and as a practical art, medicine needs to be continually revived and made more incisive through its working relations with other disciplines. Medicine in its turn is a prime contributor to aspects of man's welfare extending beyond health to remote areas of science and law, to the general benefit of social organization and adaptation. Medicine and society will both be enriched by bringing the health sciences into closer working relations with the mainstream of university research and scholarly activities. Medicine stands in need of a higher level of coordination with fundamental research in the biological and physical disciplines, engineering, and the social and behavioral sciences.

The interdependence of hitherto disparate elements of the university has now become abundantly evident. This is especially clear in relation to the most central problems medicine is facing—problems of understanding the living processes that control heredity, reproduction, cellular organization and proliferation, the hierarchy of integrative systems, individual biological development, and behavior. The most notable and lively research frontiers are those advanced through the introduction of techniques and ideas from other fields of research, e.g., the application of new physical (or other) techniques and concepts to the analysis of living processes, as in X-ray crystallography applied to protein structure, and those advanced through the convergence of two or more disciplines, e.g., the mutual reinforcement of physics, mathematics, and biology, as in the emerging field of artificial (machine) intelligence.

During the coming year we will start a systematic inquiry to determine whether or not the time is right for establishing a few models across the country, for research and research training in settings where excellence in advancing techniques and concepts can be most effectively brought to bear on health related research problems and where the convergence of hitherto isolated disciplines can be purposefully accelerated.

The general research support grant funds have helped institutions develop the better balanced research and research training programs originally envisioned, is attested by information obtained through visits to schools, from correspondence, and through other informal channels.

One school, for example, established and staffed a new experimental endocrinology laboratory. Within the next year or so, salaries paid from the grant will be picked up on the university budget, thus releasing general research support grant funds for the development of other research activities. This school also provided and staffed a new animal surgery unit for research, established an instrument development shop for the research support of several basic science departments, and undertook a pilot study on the breeding of animals for research. The same award also provided support for several students beginning their research training at the postsophomore level. Distribution of general research support grants during fiscal 1964 is expected to follow a pattern similar to that established in 1962-63.

OFFICE OF INTERNATIONAL RESEARCH

Last year I informed the committee of the establishment of an office of International Research for the purpose of coordinating the international activities of the National Institutes of Health. Under the leadership of Dr. Martin M. Cummings, this Office provides a focal point within NIH for policy formulation and guidance and coordination for all NIH international activities. This Office is also responsible for the administration of a number of programs, among which are the international centers for medical research and training, international postdoctoral fellowships, the international research associate program, and the special foreign currency program. In addition, this Office administers the NIH overseas offices which are engaged in developing and gathering information related to our foreign activities. The estimates for these programs are contained in this appropriation, with the exception of the special foreign currency program which is presented in a separate appropriation.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

The National Institutes of Health program of international centers for medical research and training has been established in response to the objectives outlined by the Congress under the International Health Research Act of 1960 (Public Law 86-610). The law seeks "to advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research and research training."

The ICMRT instrumentality represents such a cooperative endeavor, supported by NIH research grant awards to U.S. universities, in which highly stable research and research training centers have been developed at domestic and foreign affiliate sites to conduct medical investigations relevant to U.S. domestic research interests. The development of this series of international centers has created unusual opportunities for American physicians and scientists to pursue productive research careers in a foreign setting. A corollary is the stimulus the ICMRT program has provided to scientific personnel within the collaborating foreign affiliates to develop additional medical research and training resources in the participating host countries.

Each international center currently in operation consists of two basic operational elements: (1) A university-based organization devoted to a research and research training program in the United States which is closely related to the specific research and training activities conducted with; (2) an overseas counterpart facility where American scientists may take advantage of unusual or unique environmental, ethnic, and medical conditions not available for study within the continental United States.

The initial phase of the program devoted to the administratively complex task of developing foreign research facilities in collaboration with selected foreign universities and research institutions has been completed in each of the centers. All centers are now actively engaged in specific research projects.

A substantial portion of current research is focused upon the demography, epidemiology, and ecology of disease states of concern to the United States and the host nation. As the operational phase progresses, the scientific programs in each center will encompass the full spectrum of factors which directly or indirectly influence disease in the United States and abroad. These include studies of social and other environmental factors which may be related to the development and persistence of acute and chronic diseases. The presence of distinct and differing ethnic and demographic groups in foreign areas permits studies in depth of physical and biomedical factors which may be involved in racial susceptibility to infectious and malignant disease. In addition, notable progress has been achieved by each university in the creation of effective training programs for U.S. personnel at the domestic and overseas sites. Each center has been unusually successful in attracting well-trained young physicians and scientists who wish to further their experience and careers in international medical research.

In accordance with long-range ICMRT objectives, each of the programs will be conducted on a broadened basis in the future through the development of expanded multidisciplinary staffs. It was an early expectation of the ICMRT Advisory Committee that a multidisciplinary research team approach be developed within the several centers to more effectively investigate the complex bio-

medical problems which prevail at the foreign sites. As a consequence, scientific staffs are currently being developed and trained to study not only the traditional tropical diseases, but a variety of other medical conditions which exist in the countries where the centers have been established.

International postdoctoral fellowships

International postdoctoral fellowships have been awarded since 1958 to promising foreign scientists preparing themselves for careers in biomedical research. Although these fellowships undoubtedly help to build research capabilities in other countries, the purpose of the program retains a basically domestic orientation. One purpose of these fellowships is to enrich postgraduate training in the biomedical sciences in the United States by enabling foreign investigators to share their ideas and background with American colleagues. Another is to permit foreign scientists to participate in research bearing upon the health needs of the American people—research which is frequently continued and extended upon return of the fellow to his home country. International fellowships not only enhance opportunities for future collaborative research but help to strengthen research environments abroad to which American scientists may go to pursue specialized training.

International research associate program

A variety of unusual or unique opportunities exists in foreign countries to pursue studies of substantial importance to medical science and to the health of Americans. Investigations in the field of geographic pathology and epidemiology on an international basis are likely to continue to provide important clues to the causes of certain diseases which cannot be studied adequately in more restricted environments.

For example, the incidence of our two most important health problems, atherosclerosis and cancer, are substantially affected by hereditary and environmental factors, and the effect of these factors may often be studied best in foreign countries. It has now been shown that susceptibility to coronary artery disease is, in part, related to the nature of the diet. This very important finding was to a major degree confirmed by studies overseas in populations consuming diets substantially different from those of Americans. In the fields of infectious disease, nutrition, and genetics, many important discoveries of direct relevance to the health of the American people have been or could be made by exploiting unusual research opportunities in foreign lands.

To assure that there will be available in the future adequate numbers of highly capable American internationally oriented investigators to meet the needs of Public Health Service, the National Institutes of Health international research associate program is providing opportunities for promising young scientists to work abroad as members of established research groups. This has been done by broadening the present research associate program of NIH to provide for assignment of 8-10 Public Health Service commissioned officers each year to research projects and programs overseas. This program will fulfill an important need of the Public Health Service by supplying additional highly skilled manpower.

While studies in infectious diseases are particularly appropriate overseas, each of the categorical Institutes of the National Institutes of Health has specific international interests and programs. For example, at the SEATO Cholera Laboratory in Pakistan scientists of the National Heart Institute are exploiting a unique opportunity for studying water and electrolyte depletion and repletion phenomena. Investigators in the National Institute of Arthritis and Metabolic Diseases are studying the epidemiology of diabetes in connection with nutrition surveys in foreign countries. International research associates assigned to such research units will be trained by senior preceptors while performing needed professional services. The funds requested will provide for the support of approximately six research associates next year. Recruitment has been most effective and 8-10 new associates have committed themselves for this program during the subsequent fiscal year.

Overseas offices

Since the nature, scope, and magnitude of the U.S. effort in international health science had been incompletely assessed and evaluated, it became necessary for the NIH to establish, with the approval of the Bureau of the Budget, overseas offices under the supervision of the Office of International Research. NIH offices have been activated in Paris, France, Rio de Janeiro, Brazil, and Tokyo, Japan.

In addition, representatives are on duty in London, England, and New Delhi, India.

In order to properly evaluate our investment abroad, it is necessary to consider the aggregate effects on science ecology within a given country, as well as the scientific merit of all research proposals.

Continuous on-the-scene appraisal of our programs will permit us to choose selectively those activities best calculated to advance our mission in the most effective and economical manner.

The NIH representatives have the following responsibilities :

(1) Advance the program and policy interests of the NIH, and the scientific knowledge, training, and research objectives of individual U.S. scientists or U.S. scientific institutions.

(2) Execute NIH responsibilities in respect to active, pending, or planned research projects, and in relation to research objectives generated through the NIH intramural or extramural programs.

(3) Participate in assessing the value of international meetings to decide which should have NIH representation and what type of representation would best serve the interests of NIH and its programs.

(4) Provide NIH with information on scientific interests, capabilities, and resources available in other countries to solve mutual problems and promote mutual interests.

Although our overseas offices have been activated only a short period of time, significant information has already been accumulated in regard to our investment in the United Kingdom, Sweden, France, Israel, Brazil, Chile, Peru, Japan, and a number of other countries. This information is being disseminated to our Institutes and divisions which support research abroad. This will permit a more effective review of foreign research grant applications.

The overseas science representatives have already provided important data describing the interrelationship of our scientific effort with that of other countries. They have performed site visits for special purposes reducing travel requirements from this country to acquire the same information. They have also provided data which permits a more realistic understanding of the problems which are associated with foreign relationships. Finally, through liaison with the State Department science attachés they have been able to assist in providing a better image and understanding of United States as well as NIH science policies.

Conclusion

In conclusion, Mr. Chairman, the request for General Research and Services is \$164,674,000, compared with \$154,564,000 for last year. The attached table shows the activity distribution as related to the administering organizations.

Mr. FOGARTY. The appropriation for 1963, adjusted for comparability, is \$154,896,000, and the request for 1964 is \$165,674,000, an increase of \$9,778,000 and 79 positions.

APPROPRIATION STRUCTURE

This is all one appropriation, but we have three—what do you call them, three divisions?

Dr. SHANNON. Three activities.

Mr. FOGARTY. If these are separate and distinct activities, and you seem to treat them as such, why shouldn't we have a separate appropriation for each activity instead of one overall appropriation?

Dr. SHANNON. This we would be glad to discuss with the Department.

Mr. FOGARTY. It seems to me that you treat them as separate programs—the National Institute of General Medical Sciences, the Division of Research Facilities and Resources, and the Office of International Research. Is there any particular reason why they are all bunched together under one appropriation?

Dr. SHANNON. I don't believe that there is any particular reason, except that it has been the general policy of the Department, as I understand it, to limit the number of appropriations to the extent feasible.

Would that be correct, Mr. Kelly?

Mr. KELLY. I think there is an argument as to whether or not it is advisable to have a great many appropriations. We did this year, at the committee's suggestion, take out biologic standards because it does not essentially relate to the research mission of the NIH and was an operating program that deserved special attention.

All three of these activities, I think, do fully relate to the research and research training mission of the NIH, but they could be divided up and acted upon separately.

Mr. FOGARTY. But the Division of Research Facilities and Resources, and the Office of International Research are not very closely related, are they?

Mr. KELLY. No. What we have done is we have taken all the non-categorical activities—

Mr. FOGARTY. I just raised the question. I am not ready to say it should be done now, but it seemed to me in listening to the opening statement that these are three rather distinct programs.

Dr. SHANNON. Mr. Fogarty, as the programs evolve, I am quite sure that, with the Institute of General Medical Science now reaching full Institute status, this will require separate consideration, parallel with the other Institutes. I do not believe we have discussed this with the Department yet. I do not believe there would be any difficulty in setting this out. I think that one of the problems of the Division of Research Facilities and Resources is that this activity is really supported by two appropriations, one of which is research facilities construction; the other is this more general operating appropriation.

It is difficult to see how we can put a specific construction authorization into a broader organization. But we will inquire into this matter, discuss it with the Department, and perhaps make a proposal.

BUDGETARY RESERVES IN NIH

Mr. FOGARTY. What 1963 funds are being held in reserve?

Mr. SEGGER. \$25,400,000, Mr. Fogarty, is the total.

Mr. FOGARTY. I asked the general question yesterday, because it appeared in some of these articles that we mentioned that you are not going to use \$25 million.

Dr. SHANNON. Mr. Fogarty, as I said yesterday, in response to the direct question, we have not felt under any political pressures to obtain funds that we were not convinced scientifically could be used effectively in the support of sound research and research training, and I think this appropriation and the balances that will accrue—the moneys that are now in reserve—might be used as an example of that, especially when a very careful study of the appropriation last summer—I believe we obtained the appropriation in September, did we not?

Mr. KELLY. I think so.

Dr. SHANNON. Do you remember the specific date?

Mr. KELLY. No.

Dr. SHANNON. We faced the need to develop a program for budget execution that involved an annual expenditure of funds, made available by Congress, but with a period of only 9 months in the program development. I might say this is one of our repeated difficulties in attempting to develop a year's activities within substantially less than a year's time.

HISTORY OF RECENT INCREASES IN THE BUDGET

Mr. FOGARTY. I notice from a table we had prepared, that the House of Representatives has never been responsible for passing a bill that provided more funds than you could use to advantage.

Dr. SHANNON. This is correct, sir.

BUDGET RESERVES

We proposed to the Department that an operational budget be made available which envisions putting into reserve an unprogramed amount, in round figures, of \$25 million. I am not prepared to give these figures specifically, but they are substantially correct.

On quite extensive discussion with the Department, we came out with funds being put in reserve substantially what we had recommended ourselves. In addition, as I recall, there was about \$2 million put in reserve by the Bureau of the Budget.

Is that the figure?

Mr. KELLY. I don't recall.

Mr. SEGGER. Roughly, about 2 or 3 million.

Dr. SHANNON. Well, the point is that our best judgment on program opportunities and program needs in terms of the expenditure of something in the order of magnitude of well under a billion, but a very large sum, was agreed to in general by the Department and by the Bureau of the Budget, and we developed our program on the basis of not being able to plan the expenditure of about \$25 million.

Now, this is a situation that is not very different than what we have met in previous years. These funds are put in reserve with the understanding that if we have urgent needs and if the program evolves in such a way that it can be shown later in the year that these funds can be put to work in a highly effective way, then we will have the opportunity to approach the Bureau of the Budget for relief.

We are given further freedom in this reserve system, in that within the total dollar funds that are made available it becomes possible to pull one item out of reserve, and balance it with another item, going into reserve.

Now, this is terribly important, because in a complex program such as ours, that is budgeted in so many activities, you very frequently will develop balances in one place and deficits in another. In our own operating program at the present time, we take all the activities at midyear, and appraise what will be the subsequent cost of our activity. We find that there is an aggregate accumulation of deficits in terms of approved research grants: approved training grants: some funds in the direct operation: some contract money and the like, that amounts to about \$17 million.

On the other hand, in other activities obtained within the budget, as best we can judge now, there could be up to roughly \$25 million for our use and we are in the process now of attempting a readjustment within the activity structure of funds, so that we can come out with the best program possible, within the dollar limitation available.

In some cases modification of use of these funds will involve taking funds from the grant area, and putting them in the contract area; and in cases such as this, we systematically, as you know, have informed the committee of our intent, so that the committee can take exceptions to the proposal if they feel such modification of fund distribution is unwise.

OPERATING PRESSURES

Now I think, sir, the only pressures that we operate under in the NIH are the pressures of circumstance, which place before us the goal of solving very serious disease; very serious chronic illness under a situation where the dearth of our knowledge or the depth of our ignorance is substantial. So I think the pressures that we work under are largely professional pressures rather than political pressures.

I will add a third, the administrative pressures.

We talked at some length yesterday of some of the problems in the grants administration area, that really are with us on a day-to-day basis. They are very real pressures, both upon us from the Congress, and upon us from the school and upon us from our own beliefs in the need to strengthen our administrative procedure; but of these three sources of pressure, I must say I am not conscious of political pressure.

CHARGE THAT UNSOUND PROJECTS ARE BEING FINANCED DUE TO FUND SURPLUS

Mr. FOGARTY. Well, the charge has been made that you are scraping the bottom of the barrel; that you have been looking for applications to fund.

That is not so?

Dr. SHANNON. Well, sir, that charge is untrue.

PROCEDURES FOR MAKING RESEARCH GRANTS

If you have very inadequate money in terms of funds available so that you can only pay a very small percentage of the research grants, then obviously, the average priority scores that are paid, is very high, in terms of relative merit; but our general procedure that determines what we will pay and what we will not pay involves, as we have explained to the committee on previous occasions, involves a dual judgment, the initial judgment being whether a study warrants support or does not warrant support.

I might say this judgment is made either by a study section or by the advisory group established in association with the Division of Research Grants.

The second judgment is determined by as objective a way as possible, the rank order of priority, so that in those appropriations that have had inadequate funds to pay all they feel is desirable to pay, some selection among the approved grants can be made.

I believe that the priority system is about as good a system as one can devise. On the other hand, it has broad imperfections. The priority system is very effective in placing within, or in front of a group, a large number of applications; placing a few of them in the extraordinary degree of excellence; a few of them in a more questionable, but nonetheless supportable area; and then grouping the bulk of them in what, one would say, were good, solid, judgment decisions, but where it is difficult to arrange them in the middle. But if priority scores are used for comparative purposes, to compare one year's activities with another, then they fall down.

I will point out though, for what use it is, that year after year we have analyzed the activities of our study sections in terms of what they approve and what they disapprove. As years have gone by they tend to disapprove a smaller percentage of the research projects, and a substantially lesser percentage of the research dollars that come in as wholly new applications.

Within the approved projects, the priority distribution continues to be pretty much the same from year to year. We can detect no relaxation or confusion of technique.

As I pointed out early in the hearing, we have a special procedure that gives special treatment for the lower 10 percent of the approved applications, on the assumption that if we are supporting any marginal research, it probably will be in this lower 10 percent, rather than in the higher priority material. And in some activities, in the lower 10 percent, and in the case of—I had the occasion to go over this in terms of the last 2 years of council action—some institutes will pay the bulk or recommend the payment of the bulk of the applications that fall in this lower 10 percent. Others will recommend a small percent; but this is based on individual appraisal, and if you take the action of the Heart Institute as an example, there is no general pattern to their action. Depending upon what is contained, they may pay the bulk the following meeting; depending upon what is contained in the lower 10 percent, they may pay very few.

I think this is what one would guess would happen, if relative action was brought to bear on such material.

So that now, the truth of the matter is, if one has approvable or approved projects amounting, in a given appropriation, to \$100 million, and one only has an appropriation of \$50 million, then our priority system, if it works at all—and we believe it does—would provide, in the case of a less amount of funds, the payment of research projects that are best judged as having relatively high merit; but sir, when one attempts to go beneath such a general judgment as that, I think one undertakes an unprofitable study.

PERCENTAGE OF GRANT APPLICATIONS REJECTED

Mr. FOGARTY. How many applications for grants are turned down, on an average?

Dr. SHANNON. I think, this current year, it was around 50 percent.

Mr. SEGGER. Around 47 percent were approved.

Mr. FOGARTY. 47 percent approved?

Mr. SEGGER. 53 percent turned down. This is an average.

BUDGETARY RESERVES

Mr. FOGARTY. In your professional judgment, could the funds in reserve be used to advantage for any of this institute's activities? You know, our committee has, especially in recent years, refrained from specific earmarking of funds, so you do have some leeway in transferring within an appropriation.

Dr. SHANNON. Yes, sir. This has been very valuable.

Mr. FOGARTY. That would help take care of some of these inequities that show up.

Dr. SHANNON. Yes, sir.

Mrs. FOGARTY. I just asked you, in your professional judgment, could they be used to advantage for any of this Institute's activities.

Dr. SHANNON. These are the funds in reserve. I would like Dr. Powell to answer that.

Mr. FOGARTY. All right, Doctor. Go ahead.

Dr. SHANNON. On the appropriation aspect of the question.

Dr. POWELL. In terms of research grants, as you know, sir, there is still one council meeting to go; we are not able to project exactly, but it is our best estimate at the moment, that the funds appropriated for the Division of General Medical Sciences will permit the approval of all research grants by the end of this fiscal year, so that such a transfer is not required.

Mr. FOGARTY. You have funds in reserve, don't you?

Mr. KELLY. \$332,000, I think.

Mr. FOGARTY. That is in what category?

Dr. POWELL. That is in the special programs.

Dr. SHANNON. No, I don't think so.

Mr. FOGARTY. In the justifications, you have under "Obligated balances," \$332,000.

What does that mean?

RESERVES FOR SAVINGS

Mr. KELLY. Out of the \$25,403,000 there is \$332,000 in reserve, in this account. As a matter of fact, this is a reserve. I would have to get you a specific explanation of this, but I think this is a reserve that is for savings—\$2,204,000 of the reserve is assumed to be a reserve which we would never have to take out, while \$23,199,000 of the NIH reserves are tentative reserves pending the outcome of the reexamination at this time of the year.

Mr. FOGARTY. This \$332,000 would be forced savings then?

Dr. SHANNON. Mr. Fogarty, I am not sure at this point in time, that in this appropriation, it will be.

Mr. KELLY. I think the only part of the savings that could be ascribed to the concept of being forced savings, was two decisions which were made by the Secretary, which occasioned a nominal reserve which was somewhat different than those proposed by NIH.

One of these decisions was that NIH was subject to a 3-percent reduction in the authorized staff and the dollars associated with that 3-percent reduction had to be reflected in the apportionment action; and the second was that all the cost of the pay increase and all the other personnel emoluments enacted by the Congress, had to be absorbed within the funds appropriated.

COSTS ABSORBED IN 1963

Mr. FOGARTY. In addition to the forced reserve for savings, find out how much in increased cost you were forced to absorb in 1963.

Dr. SHANNON. Well, sir, we can give you a breakdown of that. I don't have that with me.

Mr. SEGEL. It is roughly \$2 million, Mr. Chairman. In 1963, the pay cost absorbed is about \$2 million and in 1964, it will be about \$4 million. Of course, we are projecting for a full year in 1964.

I believe \$2,108,000 is the figure for 1963.

COMPREHENSIVE ANALYSIS OF INSTITUTION ORIENTED PROGRAMS

Mr. FOGARTY. In our report last year, we asked you to prepare a comprehensive analysis of the institution oriented programs. We have the reports you prepared, and will place them in the record.

(The reports follow:)

CLINICAL RESEARCH CENTERS

INTRODUCTION

This report concerns the concepts, goals, present status, and projection into the future of the Public Health Service's nationwide effort to increase the national level of clinical research into human diseases and to gain new insight concerning the fundamental biological conditions and problems of man.

INITIAL GOALS

The National Institutes of Health extramural clinical research centers program was started in the fall of 1959 (following recommendations by Congress in connection with the fiscal year 1960 appropriations act) to lift quality of clinical research and to put laboratory research to use much more rapidly.

Through grants to private and public institutions the program seeks both to improve and expand the level of clinical research in diseases and to obtain new knowledge concerning inherent, human body metabolism. At this early stage of the program, indications are that the hope will be realized. All clinical research center grant applications are reviewed and recommended by the appropriate national advisory councils.

GENERAL CLINICAL RESEARCH CENTERS

PROGRAM BACKGROUND

The initial appropriation for implementing the general clinical research centers (GCRC) program in the Division of General Medical Sciences amounted to \$3 million which was made available through earmarked appropriations of \$500,000 to each of six National Institutes. After this modest beginning, it became apparent that the same approach could advance similar goals in the categorical Institutes; hence these too are now included in the overall Public Health Service clinical research centers program.

Responsibility for organizing and operating the general CRC program, initially assigned to DGMS, was transferred to the Division of Research Facilities and Resources (DRFR) in July 1962, when that Division became operative.

Approximately 2½ years have passed since the first general clinical research center awards were made in May 1960. The growth of the program may be noted from attached table 1. This program is relatively young, still evolving and still undergoing revisions in its policies and guidelines. But, while these have changed somewhat and will be under continuing review for additional modification as new experience is gained, the basic concept of the program is still centered around discrete, multidepartmental, multicategorical facilities, operated by institutions qualified to conduct meritorious clinical investigations. Location of the general program within DRFR permits greater cooperation and coordination with other Division activities, all of which are related both from the standpoint of a medical research institution's total needs and the overall responsibilities of NIH. (Clinical research activities of categorical nature are centered now in the seven categorical Institutes. Their reports follow that of the general clinical research centers.)

TABLE 1.—*Growth of the general clinical research centers program*

Fiscal year	Appropriation	Cumulative total at end of each fiscal year					
		Number of centers	Approved number of beds	Number of beds available in centers admitting patients	Number of centers admitting patients	Number of institutions	Number of States
1960-----	\$3, 000, 000	8	116	-----	0	8	8
1961-----	8, 000, 000	32	479	148	13	31	21
1962-----	27, 000, 000	56	739	242	32	52	1 26
1963-----	33, 500, 000	-----	-----	² 442	² 35	-----	-----

¹ Plus District of Columbia and Puerto Rico.

² As of Dec. 1, 1962.

GEOGRAPHIC DISTRIBUTION OF FEDERALLY-SPONSORED GENERAL CLINICAL RESEARCH CENTERS
December 1, 1962



CURRENT GCRC PROGRAMS

As of December 1, 1962, 50 institutions in 26 States, the District of Columbia, and Puerto Rico, have received assistance for 56 different general clinical research centers with a total of 719 beds. Thirty-five centers with 442 beds already are admitting patients. The rest are in various preparatory stages of renovation and activation. Of the 56 awards, 27 are to private institutions, 18 are to State and 11 are to city and county-supported institutions. (The attached map and table 2 show their nationwide distribution.) Total monetary investment for DRFR to date is approximately \$44 million.



TABLE 2.—Activation and status report on general clinical research centers awards

State	Institution	Grant number	Date of initial award	Number of beds		Date of permanent unit	Date of temporary unit
				Permanent unit	Temporary unit		
Alabama	University of Alabama Medical Center	FR-32	November 1960	12		June 1962	
Arkansas	University of Arkansas	FR-49	May 1961	12		November 1961	
California	Children's Hospital, Los Angeles	FR-86	June 1962	8			
	University of Southern California	FR-43	May 1960	10		April 1961	
	University of California, San Francisco	FR-79	May 1962	15			
	do	FR-83	June 1962	9			
	Stanford University	FR-81	May 1962	6			
	do	FR-70	June 1962	31			
Colorado	University of Colorado (Children's Center)	FR-69	January 1962	4		February 1962	March 1962.
	University of Colorado	FR-51	May 1961	10			April 1961.
Connecticut	Yale University, School of Medicine	FR-38	November 1960	20	8		
Florida	University of Florida	FR-82	June 1962	10		October 1962	
Georgia	Emory University	FR-39	May 1960	16		January 1961	
	Medical College of Georgia	FR-61	May 1961	10		February 1962	
Illinois	University of Chicago	FR-55	do	29		August 1961	
	University of Illinois	FR-45	January 1962	10		January 1962	
	Northwestern University	FR-48	May 1961	14			
Indiana	University of Indiana	FR-57	January 1962	7			
Iowa	State University of Iowa	FR-59	May 1961	20	8		December 1961.
Kansas	University of Kansas	FR-67	January 1962	10			
Maryland	Johns Hopkins University	FR-35	May 1960	21		August 1960	
	Johns Hopkins University (Children's Center)	FR-52	May 1961	6			October 1961.
Massachusetts	University of Maryland	FR-33	November 1960	10			
	Harvard Medical School (PBB)	FR-31	do	24		October 1961	
	Harvard Medical School (BOH)	FR-76	June 1962	20			
	Tufts University	FR-54	May 1961	14		April 1962	
Michigan	University of Michigan	FR-42	May 1960	20		May 1962	
	Wayne State University	FR-74	June 1962	6			
Missouri	Washington University (St. Louis)	FR-36	May 1960	15		October 1960	
	Washington University (Children's Center)	FR-36	January 1962	8			
New Jersey	Secton Hall College of Medicine	FR-41	November 1960	20	8		June 1961.
New York	Albert Einstein College of Medicine	FR-50	May 1961	20			
	Albert Einstein College of Medicine (aeutec)	FR-66	June 1962	6			
	Cornell University Medical College	FR-47	November 1960	20		April 1962	
	Montefiore Hospital	FR-53	May 1961	13			
	New York University-Bellevue Medical Center	FR-96	May 1960	12	8	December 1961	December 1961. November 1960.
	New York University-Bellevue Medical Center (Children's Center)	FR-96	July 1961	8			
	University of Rochester	FR-44	November 1960	8		January 1961	
	State University of New York at Buffalo	FR-77	June 1962	8			
	State University of New York Research Foundation (Upstate)	FR-85	do	10	5		

Because clinical or bedside studies of man and his diseases require a great deal of cooperation on the part of the patient, and very careful control of his diet, the medicines administered, special nursing attention, and many laboratory tests, the cost is higher than for ordinary hospital care. Adjacent laboratory space, specialized equipment, treatment rooms, diet kitchens and specialized personnel are requisite. The size of the centers has ranged from 6 to 31 permanent beds, 0 to 7 core laboratories, and from about 2,000 to 15,000 gross square feet.

Administration of each center is accomplished through a full-time director working with an interdepartmental supervisory committee appointed by the sponsoring institution. Extraordinary teamwork is essential, involving hospital authorities and staff, scientific and medical investigators, and medical school administration. Apparent to all those working on the program is the tremendous surge of enthusiasm engendered by the new opportunities and challenges offered, not only for the advancement of medical research, but in patient care, administrative matters, and medical education and training.

TYPES OF GENERAL CLINICAL RESEARCH CENTERS

A number of different varieties or models of centers already are included within the current program. They are concerned with different populations of patients which directly affect the nature of the facility and equipment needed. Forty-eight are adult or mixed adult-children centers; eight are for children only; one is solely for the study of premature infants; and one is a center for acute problems. The latter is at Albert Einstein College of Medicine and its research program includes studies of shock, trauma, burns, and sepsis, as well as studies on pre- and post-operative patients. Portions of the physical facility are in the operating room. Monitoring and other special equipment are an important part of the program.

POLICIES AND GUIDELINES

Experience thus far in the GCRC program has shown that patients admitted in connection with ongoing research projects receive the finest care known to medicine. No treatment is ever given that does not offer hope for the patient's physical or mental betterment. This has made the general clinical research centers very popular among prospective patients and has helped insure essential patient cooperation.

Although each center has its own administrative rules and regulations, the following general guidelines apply to all:

(1) Funds provided by GCRC grants may be used for personnel, needed equipment and supplies to be used in the center only.

(2) Only research patients are admitted to clinical research centers. They may remain at a center only while they are, in fact, research patients. While there, they agree to assist research physicians in achieving stipulated research goals.

(3) Clinical center programs must be administered by a program director and an advisory committee appointed by the sponsoring institution.

(4) Hospitalization costs of research patients are borne by center grants. It is left to each institution to take all reasonable precautions to insure that research programs accepted for study are worthwhile, offering reasonable expectations for the gain of useful knowledge; to operate each center as a full-fledged institutional resource (not for advancing the private projects of any one researcher or limited clique of investigators); to properly administer its policies so that high standards of medical ethics are maintained and the finest possible medical care provided; to insure a stable paramedical staff and complete hospital services; and to include among its records, documentation that each patient accepted is truly a research patient. The impact of these clinical centers programs is important nationally. In addition to research itself, there has proved to be efficient multiple use of the centers for research training purposes.

COORDINATION WITH OTHER INSTITUTIONAL PROGRAMS

The general clinical research center program provides funds for meeting the total costs of renovating existing space in medical institutions, where centers are to be established. However there are instances where existing space is unavailable or insufficient. Therefore plans for new centers usually involve

allocating part of a newly constructed building, or building a new addition on to an existing structure. Because new construction cannot be financed by this program, required space can sometimes be gained through matching funds under the Public Health Service research facilities construction program. The general clinical research center and the health research facilities construction programs coordinate well in answering such needs at such institutions as the University of Maryland, University of Iowa, and Vanderbilt University.

PROGRAM ACCOMPLISHMENTS

Throughout the history of this program, the criteria of evaluation of applications have been: (1) Quality of the research proposed for the center including the capability and potential of the investigative staff; (2) soundness of the administration proposed for the center as well as soundness of climate at the institution, for such research; (3) quality of the physical aspects of the facility proposed; and (4) appropriateness of the budget. Of these the major criterion is research capability and potential.

NIH responsibilities relative to this program have included from the very beginning visits by staff members of the general clinical research centers branch prior to the submission of an application, negotiation of the initial and each continuation year's awards, and liaison visits by the staff to ongoing centers. Through these staff roles, optimal channels of communication have been sought and found.

Some idea of the research accomplishments involved can be gained from the following samples that have been selected from a long list of reported results.

Muscular dystrophy has been linked to disturbances in metabolism by high-energy phosphates. Special compounds of nucleic acid may be of therapeutic value.

The first instance of genetic inborn error involving ability to metabolize short-chain fatty acids has been uncovered.

Use of a transistorized "pacemaker" for stimulating the heart with radio waves has proven to be practical on seven patients with heart block. (Using the same method of study, heart output at varying radio-controlled heart rates allows determination of the optimal heart rate for each patient.)

Certain lung cancers have been found to secrete a polypeptide which stimulates production of large quantities of adrenal cortical steroids leading to severe Cushing's syndrome, a condition characterized by obesity, muscle wasting, skin atrophy, salt and water retention, etc.

Use of the artificial kidney has proven its ability not only to save lives but to maintain the health of selected patients for as long as 2 years.

A method of determining the lifespan of human blood platelets was developed and applied to studies of blood-banking and diseases associated with abnormal bleeding.

It has been demonstrated that the anemia and hemolytic tendency of most patients with paroxysmal nocturnal hemoglobinuria (the periodic nightly appearance of red blood cells in the urine) can be corrected with iron and anabolic steroids.

Development of a laboratory screening test for primary cancer of the kidney or bladder.

CLINICAL RESEARCH HIGHLIGHTS

As expected, the initial expenditures of money and effort for new centers went into providing "bricks and mortar" to renovate available facilities, and initial studies to get each center underway. Scientific papers resulting from research accomplished at these centers are now beginning to appear.

Some idea of the work being done can best be illustrated by excerpts from a few sample progress reports previously noted. The following are offered:

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD.

The Johns Hopkins Clinical Center was opened August 1960 with 21 beds. As of December 1961, 60 research projects had been started involving a total of 354 patients admitted for studies covering 4,811 patient days.

Medical projects undertaken were in radiology, endocrinology, metabolism, cardiology, gastroenterology, hematology, surgery, physiology, dermatology, genetics, urology, pharmacology, and neurology.

They included studies of Sjogren's syndrome (a drying of mucous membranes); iodine uptake of the thyroid gland; muscular dystrophy; the mechanism of protein excretion by the kidneys; effects of gluten-free diets; body composition of patients on long term steroid therapy; cancer chemotherapy; magnesium balance; systemic mast cell disease; hypertension; coronary artery disease; chemotherapy of abnormal growth diseases; and epilepsy.

Papers published or to be published or presented by investigators of the center include the following:

Criley, J. M., and Ross, R. S.: "Mitral Valve Function in Man." Presented at the 34th Scientific Session, American Heart Association.

Prokipchuk, E. J., Bayless, I. M., Iber, F. L., Hendrix, T. R.: "Xylose Absorption, Distribution, and Urinary Excretion in Cirrhosis." Presented at the eastern section meeting, American Federation for Clinical Research.

Ross, R. S., Criley, J. M., and Morgan, R. H.: "Cine Angiocardiography in Mitral Valve Disease." Transactions of the American Association of Physicians. (In press.)

NEW YORK UNIVERSITY MEDICAL CENTER, NEW YORK, N.Y.

The general clinical research center at this institution was opened in Bellevue Hospital in October 1960 in a temporary unit with six beds. The permanent unit with 12 beds opened in December the following year. A total of 27 clinical research projects had been started as of December 31, 1962, involving 100 patients for a total of 915 patient-days.

These projects included clinical research on burns and efforts to develop new forms of therapy. From January through June 1961, five burn patients were admitted for study. One had suffered burn injuries to his lungs. Two others suffered moderately severe third-degree burns. Two others had severe third-degree burns over more than 50 percent of their body surfaces. Out of the studies of these patients there developed additional information on the efficacy of penicillin as a single antibiotic and on the use of the hypothermia mattress as a means of controlling temperature in burn cases.

Other projects at the center included studies of the effects of human growth hormone injected locally at the site of chronic indolent ulcers; disorders of potassium excretion; kidney diseases; hypertension; lipid metabolism; total bile and pancreatic juice secretion in certain patients; the surgical interruption of portions of sympathetic nervous pathways to relieve pain in the hip and knee; rheumatoid lung disease; rheumatoid arthritis; and the effects of metabolic defects in vitamin D-resistant rickets.

Papers published, or to be published or presented by investigators of the center include the following:

Gershberg, H.: "Renal Effect of Parathyroid Extract." Annals of the New York Academy of Sciences, February 1962.

Newmann, L., Mari, S., and Gershberg, H.: "Human Growth Hormone in Vitamin D-resistant Rickets and Achondroplastic Dwarfism." Federation Proceedings, March 1962.

Mari, S., Burton, B., and Gershberg, H.: "Hyperthyroidism, Acetylation and Serum Cholesterol." Clinical Research. (In press.)

Sklar, B., Seegers, W., and Hirschhorn, K.: "Hyperlipemia." Geriatrics, August 1961.

Rothfield, N.: "Clinical and Pathological Studies of Lupus Nephritis." Presented at the New York Rheumatism Association meeting, April 1962.

Gombos, E., Bopp, P., Hulet, W., Goldring, W., Balwin, D., and Chasis, H.: "Reactivity of the Renal and Systemic Circulations to Vasoconstrictor Agents." Journal of Clinical Investigation. (In press.)

Wesson, L.: "Diurnal Cycle of Glomerular Filtration, Renal Plasma Flow, Plasma Concentrations and Excretion Rates of Sodium, Chloride, Potassium, Magnesium and Phosphate in Healthy Young Men and Women." (In preparation.)

Vagnucci, A., and Wesson, L.: "Diurnal Cycle of Glomerular Filtration, Renal Plasma Flow and Plasma Concentrations of Sodium, Chloride and Potassium in Hypertensive Patients." (In preparation.)

Wesson, L.: "Glomerular Filtration and Aldosterone Secretion Rate During Changes in Dietary Salt Intake in Man." (In preparation.)

Pastorelle, D. J.: "Regulation of Physiologic Arteriovenous Communication in Man Demonstrated by Hydrocortisone Infusion." *Circulation* 24: 1012, 1961 (abstract).

UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, PHILADELPHIA, PA.

A temporary clinical research center of 5 beds was opened in November 1960 and a permanent unit of 10 beds opened in February 1962. As of December 31, 1961, 22 research projects had been initiated involving 115 research patients admitted to the center for a total of 1,505 patient-days.

Among projects undertaken was an extensive study of a family in which the parents were mentally normal but whose six children demonstrate varying degrees of retardation and bizarre behavioral development. Using a technique developed at the university for analyzing chromosomes, investigators of the center found that four of the children had a fusion of two of their chromosomes. This condition also was found in the mother's cells but not in the cells of the maternal grandmother. A fifth child has normal chromosomes and the sixth has an extra chromosome and the physical stigmata associated with mongolism. The investigators believe the chromosome anomalies probably are due to metabolic errors. They are seeking to determine exact causes. The work has the potential for offering a new insight into metabolic disturbances associated with mental retardation and may aid in the development of diagnostic and therapeutic measures to prevent or reduce such retardation.

Other projects at the center include studies of antibody response in patients with cancer; the regulation of the volume and composition of body fluids by the kidneys and endocrine glands; porphyrin, calcium, and phosphate metabolism; the mechanism of lipemia; and improved surgical techniques in connection with disorders of the bladder.

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE, SEATTLE, WASH.

This center, located in the Teaching and Research Hospital of the University of Washington, was opened in July 1960 with 12 beds.

Through 1961, 196 patients had been admitted to the center for a total of 2,604 patient-days, providing data for 39 clinical projects.

Specific research projects include the development of a method of rehabilitating, with the artificial kidney, selected young adults who otherwise apparently would die of kidney disease. Of eight patients on whom the method has been used, seven are well. Three of these patients have undergone 2 years of treatment. The study is the first successful attempt to use the artificial kidney to maintain health over such prolonged periods of time. This could lead toward large-scale application of this form of therapy, conceivably rehabilitating hundreds of patients every year.

In other research activities, the center is investigating the physiologic controls of pancreatic digestive secretion; studying the mechanisms of the brain's control of respiration in patients having various brain and spinal cord diseases; investigating the pathways of fat metabolism in diabetic subjects and in the extremely obese patient; studying familiar inheritable diseases, with emphasis on the detection and better understanding of the mechanism of biochemical derangements; and investigating the unusual primary diseases of the bones which cause collapse and debility.

In another study, the center is carrying out heart catheterization studies of special types to (1) appraise quantitatively the actual results in the performance of the heart produced by newer operations for valvular heart disease; and (2) study the need and use of specific nutrients by the heart muscle itself, such as blood fat and carbohydrate.

PROGRAM PROJECTIONS

It is anticipated that by the end of fiscal year 1963, there will be about 70 centers and by the end of 1964, about 80.

Applications for a new variety of general clinical research center, viz.: a maternal-child clinical research center, are anticipated. For those institutions wherein there is considerable research activity relative to the study of the pregnant woman and the newborn child, such a center may have unusual advantages. One of the most important questions affecting the development of the general clinical research centers program will be whether or not centers for outpatients will be permitted as a distinct type of general clinical research center. This is under review by the NIH. If an affirmative decision is reached, it will undoubtedly appreciably increase the size of the program, the amount of followup on discharged center patients, and the quality of clinical research on outpatients. Such a program also has the potential for furthering clinical research training. The different types of general clinical research centers that have now been developed as well as those being considered represent a diverse and fruitful harvest. To date, only two non-university-affiliated hospitals have been approved for a general clinical research center. Undoubtedly, others will be applying successfully during the next few years.

CLINICAL RESEARCH CENTERS PROGRAMS OF THE CATEGORICAL INSTITUTES

THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Program background

Clinical research activity of a categorical nature involving National Institute of Arthritis and Metabolic Diseases administration was first authorized by an appropriation of \$500,000 in the fiscal 1962 budget.

The report of the Senate on DHEW appropriations for 1963, page 42, states: "A clinical research center program for arthritis and metabolic diseases was inaugurated last year. However, the Institute was only allotted \$500,000 for these centers and the committee was informed that there is now a considerable backlog of high-quality applications. The centers program is proving so effective in other areas of research that the committee is convinced that much progress would result from a substantial expansion of research centers and program grants devoted to attacks on arthritis, diabetes, and many disorders of the blood, liver, and bone. The committee, therefore, recommends \$2 million above the House allowance for these categorical research centers."

Current program objectives

Increasing opportunities and capabilities for high-quality clinical investigation suggest the need in a number of institutions for support of facilities for such research in each of our several categorical areas. It is obvious, however, that establishment of separate units of this type for each program area in every institution possessing the necessary potential would create administrative problems and some duplication of effort. For these reasons, NIAMD extramural responsibilities in clinical investigation are being fulfilled largely (1) through a heavy dependence on the general clinical research centers supported by DRFR for the facilities, and (2) NIAMD project and program-project support for research substance. In order to meet completely our total categorical needs, however, a relatively small but complementary program of rather specialized clinical research units has proved to be highly essential. This is a very logical program to meet a situation which finds a number of institutions limited to a specific disease field or having definite strength, particularly in investigative skills at the clinical level, in only one or perhaps two divisions of medicine. In such circumstances, a general center would be most inappropriate.

The specific areas recognized by this Institute and requiring potential special consideration are: arthritis, dermatology, diabetes, endocrinology, gastroenterology, hematology, metabolism, nutrition, and orthopedics. It is already of record that each of our presently active grants for categorical centers involves generally only one area. It seems most realistic to think of the likelihood of four to eight grants in each of these separate areas, scattered over the United States within the next 5 years, although the rate of particular expansion of any given area cannot be reliably predicted.

NIAMD present program through Nov. 30, 1962

Grant No.	Program director	Area represented	Fiscal year support	
			1962	1963
AM 04501-----	Bauer-----	Metabolism and endocrinology-----		\$215,868
AM 05577-----	Bayles-----	Arthritis-----	\$214,542	151,799
AM 05578-----	Flink-----	Endocrinology and surgery-----	89,213	128,489
AM 05630-----	Schilling-----	Hematology-----	142,621	115,065
AM 05760-----	Schwartz-----	Metabolism-----	35,105	45,460
Total-----			481,481	656,681

In addition there are known applications presently pending payment or being considered as follows:

Grant No.	Program director	Area represented	Fiscal year support	
			1962	1963
AM 05577-----	Bayles-----	Arthritis supplemental to present grant-----		\$39,728
AM 05578-----	Flink-----	Endocrinology and surgery supplemental to present grant-----		93,084
AM 06902-----	Faloon-----	Nutrition-----		138,855
AM 06908-----	Summerskill-----	Gastroenterology-----		92,228
Total-----				363,895

The figures shown for pending grants reflect only the amounts requested and are not adjusted for a common end date of September 30, nor do the figures make allowance for any changes in amounts which may be recommended by our advisers. March 1963 applications have not all been received in the Institute as this is written.

Scientific highlights

As a consequence of the award of AM 04501 to Dr. Walter Bauer's group, the metabolic study ward at Massachusetts General Hospital was able to operate continuously throughout the year for the first time since its inception in 1928. This was made possible by the adequacy of funds provided from the grant for patient care and by the provision of air conditioning for a portion of the quarters to permit certain temperature sensitive studies to be conducted without interruption during the summer months. As a specific example of numerous investigations in this center, studies in glyoxalate metabolism, previously investigated almost exclusively in the basic laboratories and aimed at developing techniques necessary to clinical studies, have now been extended to patients. Members of two families identified as having children characterized by hyperoxaluria and oxalosis were studied in the center beds with special metabolic techniques employing $C^{14}O_2$ and analysis of the intermediate steps in glyoxalate metabolism in their red blood cells and in tissues from liver and muscle biopsies in order to determine the nature of the disordered metabolism in these diseases.

In addition, two younger investigator members of the team under this grant have already been tapped to become directors of programs at other institutions, thus fulfilling one of the major aims of the categorical center program.

In an attempt to evaluate the role of various blood protein fractions in the pathogenesis and pathology of arthritis, the group at Robert Breck Brigham Hospital in Boston under Dr. Theodore B. Bayles is studying gamma globulin

fractions for their characteristic interactions. Certain technical methods of serology are being applied to materials derived from arthritis patients to advance studies of diagnostic procedures in rheumatoid arthritis. These methods would be useful for differentiating various types of arthritis, for evaluating the usefulness of certain body substances in predicting likelihood of occurrence of arthritis, and for estimating the progression of or sequelae in active disease. In certain patients with osteoarthritis and rheumatoid arthritis, studies have been performed using biopsied tissues from joints to try to uncover the reasons for leakage of blood fluids and red blood cells into these areas. Information is sought to account for the differences in intensity and speed of reaction in the two conditions in hope that techniques for control may be worked out.

In considering the reported progress to date, it should be pointed out that the program is really of too recent origin to make valid assessments of accomplishment. There is agreement among our advisers and the recipients of support that the possession of categorical research facilities is the greatest single stimulus to clinical research in at least the past decade. Furthermore, the favorable influence on NIAMD-supported training activities and an eye-opening impact on scientists in more fundamentally oriented research alerting them to the problem and challenges of clinical research are indirect but definite marks of progress as well as dividends from the program.

Program projections

Looking to the future, it is anticipated that there will be a continuing growth pattern similar to that which is evident in the period subsequent to the beginning of the program. This would result in establishment of a few additional categorical centers during each of the next several years. The locations would fall primarily into one or the other of two general categories: (a) those institutions with excellent investigative resources which are more or less permanently oriented toward one or two specific NIAMD categorical areas, or (b) those which at that time would not be appropriate for a multicategorical (or general) clinical research center but in which strong research potential exists in one or more of the NIAMD fields. In the case of the latter type, the NIAMD unit might be a forerunner of a general center. Its existence for a few years in temporary status could be justified very adequately on the strength of existing NIAMD-related capabilities.

Two examples can be cited as illustrations of the probable nature of future developments. To illustrate the former category, the Hospital for Special Surgery in New York has been recognized for years as an excellent focus of clinical orthopedics and rheumatology. At the present time, changes are underway or contemplated which should create an environment for excellent clinical investigation to flourish, taking advantage of a wealth of clinical ability and patient material. When this situation matures, it should provide a natural focus for an NIAMD clinical research center. On the other hand, an application from the Upstate Medical Center at Syracuse, N.Y., furnishes an example of the second category. In this institution, the present research strength lies primarily in the areas of clinical nutrition and endocrinology. A new university hospital is in the planning stage, however, and provisions for a general clinical research unit will probably be included, when the development of competent, diverse clinical research interests indicates that it qualifies. In the meantime, expenditure of a small sum of money would permit minimal alterations in the present hospital so as to establish a six-bed research unit. This would seem to be a highly appropriate situation in which to establish an NIAMD center, justified by taking advantage immediately of existing capabilities in the two research areas mentioned as well as providing an excellent training locale for a probable general clinical research center in the future.

In summary, the NIAMD activity in support of categorical clinical research centers can best be described as one which will expand steadily but slowly, with units being established in highly specialized situations where a general center would be inappropriate but where the capability or potential for excellent clinical investigation exists in an NIAMD program area.

THE NATIONAL CANCER INSTITUTE

Current programs

The National Cancer Institute is deeply committed to support research and resources aimed at clinical approaches to the control of cancer. In fiscal year 1963, for example, it is expected that around \$17 million will be devoted to research grant support of such activities, which take many forms and involve efforts of

individuals, highly organized institutions, of widely dispersed but integrated and coordinated research activities, and of cooperative efforts of large numbers of institutions and researchers focusing on specific and defined clinical problems. These endeavors are adding to knowledge in such critical areas as chemotherapeutic treatment of cancer, and diagnosis and therapy involving the use of radiation and the related radiation physics and radiation biology; as clinical pathology and as environmental cancer, as well as in other areas where needs are known to exist.

The identification of these needs and approaches is the result of spontaneous interest and urging of the scientific community, complemented by the judgments and efforts of the National Cancer Institute and its advisers and the financial support of a number of private and public voluntary health organizations. Thus, program activities and directions should be expected to lead in many directions, and to change form and content as leads develop and are exhausted, as well as to result in flexible approaches to solutions, and to the use of varied devices of support. Thus, the efforts for the National Cancer Institute may be characterized as one of accommodating devices of support to the ends to be sought.

For many years, we have understood the profound importance of providing for comprehensive, long-range support for the clinical study of the cancer problem. This need was recognized by the Senate Committee on Appropriations. (See Rept. No. 1672 on H.R. 10904, on proposed fiscal year 1963 appropriations for NIH and other agencies.) Thus, the committee said that " * * * categorical center awards should augment the Nation's research resources by making available to investigators additional facilities and support for cancer research." We have taken account of this advice and have continued in our efforts to stimulate ideas and to seek appropriate partnerships with institutions which have the necessary competence and facilities available or which offer the prospect for effective expansion into research areas of mutual interest.

Within the framework of accommodation to program aims, support of research beds with supporting laboratories and personnel has been provided with clinical research center funds in our research grant activity. Such clinical research units for cancer make it possible to give intensive study for small numbers of patients under rigidly controlled conditions.

Program accomplishments

In addition to providing funds for the research conducted in the general clinical research centers supported by DRFR, NCI has established or is about to establish 15 cancer units in 12 hospitals (see table 3), which are associated with universities or other cancer research institutions. There are other locations where such units can be established but we believe the future will see only moderate increases in expenditures from NCI funds for such units. Cancer is not a disease that can be treated by any one medical specialty or by any one set of conditions or in any single part of a hospital. The disease is treated by radiation, surgery, and chemotherapy. Most of the clinical disciplines are involved. Some research cancer patients may need to be assigned to bed space for varied services of a medical facility rather than be concentrated in discrete research bed units. In many cases patients require extraordinary facilities associated with special clinical disciplines. For example, radiation shielding requirements often make it essential that the equipment be placed in a physical location where protective measures against the penetration of X-rays into other areas can be effected more readily. Surgical facilities, especially those involving new perfusion techniques and those equipped to perform radical surgical procedures that may sometimes be involved, are often elaborate. Also, it is frequently more acceptable to the patients, better for medical reasons, and more economical to treat many patients on an outpatient basis. Therefore, many devices are used to undertake cancer clinical research; accomplishments, then, cannot be neatly and discretely ascribed to one approach like the use of clinical research centers.

Since support for the first such units began in the last month of fiscal year 1961, and inasmuch as most of these clinical units involved recruiting and renovations before their alterations, most units have not been in full operation for a year. Therefore, it is much too early to point to accomplishments of these new units, although our preliminary evaluation is that they are meeting one of the major needs in clinical research.

Tables 3 and 4 show appropriate statistical and financial data.

TABLE 3.—*Current and proposed grants supporting clinical bed and associated laboratory units¹ as of Dec 1, 1962*

Grant No.	Institution	Number of beds	Date support began	Approximate date clinical unit began or will begin operation	Nature of research
C-3809	Memorial-Sloan Kettering Cancer Center.	² 30	-----	Mar. 1, 1962	Metabolic studies.
C-5815	Oklahoma Medical Research Institute.	8	June 1, 1961	June 1, 1961	Clinical pharmacology.
C-5826	Memorial-Sloan Kettering Cancer Center.	25	----do-----	----do-----	Cancer chemotherapy of children and adults.
C-5831	University of Texas, M. D. Anderson Hospital and Tumor Institute.	20	----do-----	July 1, 1961	Metabolic studies.
C-5834	Health Research, Inc., Roswell Park Division.	16	----do-----	Sept. 1, 1962	Biochemical metabolic and enzymestudies. Also clinical therapeutic trials and clinical pharmacology.
C-5837	Tulane University-----	10	----do-----	July 1, 1962	Chemotherapy and radiation therapy of cancer, hormones therapy, etiology of cutaneous and bladder cancer.
C-5838	Stanford University-----	³ 16	----do-----	June 1, 1961	Radiotherapy research.
C-6294	University of Texas, M. D. Anderson Hospital and Tumor Institute.	10	Jan. 1, 1962	Jan. 1, 1963	Do.
C-6295	University of Wisconsin--	5	----do-----	Jan. 1, 1962	Do.
C-6516	Children's Cancer Research Foundation, Boston.	22	Apr. 1, 1962	Apr. 1, 1962	Chemotherapy of cancer in children.
C-6518	University of Maryland---	8	June 1, 1962	June 1, 1963	Radiotherapy research.
C-6519	Yale University-----	3	----do-----	June 1, 1962	Do.
C-6551	Institute for Cancer Research, Philadelphia, Pa.	5	June 20, 1962	Apr. 1, 1963	Etiology of cancer and clinical pharmacology.
C-6749	University of Wisconsin---	⁴ 8-10	----do-----	Oct. 1, 1962	Clinical pharmacology and studies related to carcinogenesis.
C-6973	Johns Hopkins University.	22	Dec. 1, 1962	Jan. 1, 1963	Clinical chemotherapy trials; bone marrow transplantation.

¹ The term "units" is not the same as a clinical research center as used by DRFR. Each NCI "unit" includes a geographically discrete bed and/or treatment area. In most cases the beds are contiguous and within a discrete area. Associated laboratories may be for the conduct of independent investigations or for research services for the bed and treatment area and may or may not be geographically located with the bed or treatment area.

² Not fully supported.

³ Temporary center. Division of Research Facilities and Resources may support bed unit when renovations are completed.

⁴ 8 beds from Oct. 1, 1962, to Apr. 30, 1963; 10 beds beginning May 1, 1963.

TABLE 4.—*Charges for discrete clinical bed and associated laboratory units ("centers") in earlier fiscal years*

Year:	Amount
1961-----	\$2, 933, 288
1962-----	805, 392

THE NATIONAL INSTITUTE OF DENTAL RESEARCH

Program background

In the Senate report on the DHEW appropriation bill for 1963, the committee recommended that a portion of the increase be used to establish and support clinical research centers and broad research programs for comprehensive multi-disciplinary investigations. In the final appropriation for the Dental Institute, \$500,000 was allotted for categorical clinical research centers, of which \$150,000 was placed in administrative reserve, leaving \$350,000 available for 1963.

Current status

At the present time there is no specific need for funds to establish discrete hospital bed units for dental patients as usually defined for clinical research centers. Immediate program objectives are to develop some multidisciplinary research programs in clinical areas in our dental schools with a view to establishing clinical research centers. In order to develop fully the potential of dental clinical research, it is essential that some research programs be specifically oriented toward the relationship of oral disorders and total body health; and as a corollary to this it is equally important that the oral manifestations of systemic diseases be given additional emphasis.

Program projection

During the past year groundwork has been laid for initiating such programs. Up to now, only a few proposals have been received, some of which are under direct negotiation prior to awarding of grants.

During fiscal year 1963 and 1964 no more than \$350,000 will be used in this area, much of which will constitute pilot type grants.

THE NATIONAL HEART INSTITUTE

Categorical clinical research center funds are used by the National Heart Institute to support discrete clinical units consisting of contiguous beds and ancillary facilities for studying patients in broadly based cardiovascular research programs. These programs are a type of project which usually involves long-term research activity directed toward a range of problems within the area of cardiovascular disease.

Currently, there is a limited demand for these clinical resources supported by the funds earmarked for categorical centers. This situation can be attributed to (1) the increasing availability of research beds for cardiovascular clinical investigations with the rapid expansion of the general clinical research center program has minimized the need for separate categorical clinical research facilities, and (2) most investigators prefer to have the flexibility inherent in the use of nondiscrete beds, for which these funds cannot be used, so they can study pediatric, geriatric, psychiatric cases in clinical settings more appropriate than a discrete cardiovascular unit.

Following are examples of research programs which are supported in part from clinical research center funds:

1. "Studies of the relationship of emotional stress to cardiovascular disorders, particularly coronary artery disease and essential hypertension." The effect of emotional stress on the development of heart disease is a controversial question, and one which this study is attempting to answer. Under this grant, experimental studies are being carried out on research patients who are given a "stress interview" and measured for changes in the circulatory system before, during, and after such interviews.

2. "Interdisciplinary studies on atherosclerosis, with particular attention to the role of lipids." A difficult problem is undertaken in this study in determining the blood flow through internal organs. It is being studied in research patients with the use of radioactive materials to measure blood flow through the kidney and the blood vessels of the brain and the heart.

3. In another study, pumps which are placed outside the body are used to replace the function of the heart during surgery and assist the circulation in heart failure. In addition, the type of congenital heart defects which damage the lungs by increased blood flow and pressure are produced in dogs to study the manner in which the pressure affects the pulmonary blood vessels. Finally, children with heart defects are intensively studied before and after operations. Growth and development are also studied in regard to heart functions and neurologic and psychological functions are evaluated.

4. "Studies of cardiovascular diseases, with particular emphasis on improving cardiovascular surgery." Improvement of techniques for determining whether valves within the heart are functioning adequately is being undertaken in collaboration with engineers who are developing more refined methods for measuring valvular adequacy. The replacement of diseased valves by prosthetic devices is another aspect of this research which is being helped by a special plastics laboratory working on the development of valves which stimulate normal functioning.

In our judgment, the clinical resource portion of the National Heart Institute program will experience no significant growth in 1963, and it is probable that future requirements will not exceed our present total commitment of \$1,310,377, and will continue to decline in subsequent years. This trend, however, should not be interpreted as an indication of what we can expect from these projects in total, since there continues to be an increased demand for support of the basic research activities associated with the clinical research units.

TABLE 5.—*NHI projects having received support from clinical research center funds—Fiscal years 1961–63*

	Fiscal Year 1961		Fiscal Year 1962		Fiscal Year 1963	
	Total award	Clinical resource portion	Total award	Clinical resource portion	Total award	Clinical resource portion
1.....			\$196,128	\$148,669	\$237,656	0
2.....			191,664	117,725	75,841	\$32,875
3.....			456,484	218,883	233,900	192,100
4.....	\$263,224	\$136,624	285,775	102,801	367,819	104,366
5.....			111,103	101,105	108,144	39,063
6.....	274,549	216,661			227,657	28,340
7.....	315,975	315,975			245,784	103,485
8.....			230,000	192,628	241,500	114,934
9.....			65,614	38,503	105,097	52,850
10.....					321,769	66,460
11.....			261,813	191,206	186,616	99,684
12.....			81,350	45,650	84,153	84,153
13.....	129,500	119,619	683,850	144,000	547,042	176,328
14.....	462,042	309,092	506,855	0	648,359	0
15.....	498,835	195,324	870,201	0	846,833	0
16.....	199,547	166,284	360,116	0	420,394	0
17.....	41,133	15,523	61,171	0	65,371	0
18.....	78,134	21,257	75,884	0	437,951	0
19.....	453,706	335,143			375,000	0
20.....	466,651	293,551	649,385	0	683,000	0
21.....	377,600	228,100	468,450	0	468,450	0
22.....	800,000	622,800	781,106	0	800,000	0
23.....	653,709	653,709	122,733	122,733	215,739	215,739
24.....	67,067	47,267	61,587	0	68,462	0
25.....	177,866	146,126	474,871	0	487,500	0
26.....	159,070	138,945	139,360	0	175,000	0
27.....			220,059	220,059	238,651	0
28.....			190,403	138,038	210,316	0
Total.....	5,418,605	3,962,000	7,545,967	1,782,000	9,124,004	1,310,377

NATIONAL INSTITUTE OF MENTAL HEALTH

Current program objectives

As in the past, the objectives of this program at the National Institute of Mental Health are to strengthen clinical research on the etiology (including psychological, social, physiological, and biochemical factors), diagnosis and treatment (including pharmacotherapy and rehabilitation) of mental illness; on the problems of juvenile delinquency, mental retardation, aging, behavioral disturbances in children, addiction to alcohol and drugs, and psychosomatic illness.

The establishment of clinical research centers in which any of these areas would be subjected to sound scientific inquiry represents the basic objective of this program. All these areas seriously need support. More specifically, there is a search for investigators who have sufficient talent as scientists and administrators to attract other scientists to a multidisciplinary, broad, integrated attack on these problems and to develop "a stable organizational framework, an atmosphere of common purpose linking research and teaching, and an intellectual environment for research of high quality."

The hope is that the results of the investigations being initiated in this program, bringing to bear the disciplines of behavioral science, psychiatry, physiology, and biochemistry on mental illness and retardation, will prove significant. New methods of recording observations are being developed which employ modern techniques borrowed from electronic engineering, e.g., telemetry. New methods of registering and analyzing data are being developed with the aid of high-speed electronic computers. Behavioral (operant) conditioning techniques are being

used to extend the behavioral repertoire of children, 3 years old and younger, who have been diagnosed schizophrenic ("autistic"). In the current program there is an emphasis on the study of the individual subject, intensively, continuously, and over a long period of time; on developing reliable methods of quantitative, objective measurements; and on accompanying intensive clinical assessments. The types of patients vary among these centers: under study are the mentally retarded, the severely psychotic, schizophrenic children, psychiatric patients who have been found refractory to treatment, patients with psychosomatic complaints, and the chronic schizophrenic patient.

Program accomplishment

The program now supports six centers for clinical research in mental health. Three grants were awarded in the first year of the program, fiscal year 1961, obligating the available \$500,000. During the second year, fiscal year 1962, \$527,000 was awarded for three new grants, and \$255,000 for renewal and supplemental grants to ongoing centers—a total obligation of \$782,000 against the available \$1 million—with one center grant terminating because of the loss of the principal investigator. In the present year, fiscal year 1963, up to January 1, 1963, one new grant of \$172,000 has been awarded, and renewal and supplemental grants to ongoing centers have been awarded in the amount of \$643,000, for a total obligation to date of \$815,000.

Scientific highlights

This program of the National Institute of Mental Health is too new to have led to any results which can be evaluated for their significance. For example, the study patients of one of the first of these centers were only admitted on April 15, 1962.

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Program background

In fiscal year 1961, the House Subcommittee on Appropriations for NIH directed that funds be allocated for the support of specialized centers for clinical investigations in the fields represented by the National Institute of Neurological Diseases and Blindness.

In fiscal year 1962, the Senate subcommittee recommended that \$2,500,000 of the Institute of Neurology's research grant funds be used for clinical research centers. The Institute apportioned \$1 million of which \$500,000 was awarded for program projects.

For this fiscal year 1963 the Senate subcommittee directed that \$1,500,000 of the increase for research grants be devoted to the support of research centers and their complementary research program grants. This has been done.

Current program objectives

Institute program-project grants continue to support medical institutions which are engaged either in a single disciplinary approach—such as neurophysiological—to a large group of neurological and sensory disorders, or in a multidisciplinary approach to a single group of closely related disorders—such as speech disorders.

Through the coordination of interdisciplinary approaches, which may range from basic neurophysiological investigations of the nervous system to clinical neurological evaluations of diagnostic and treatment methods, it is anticipated that more effective research relationships may evolve between clinical and non-clinical research groups. Equally important, interdisciplinary approaches through program-project grants will increase opportunities for the translation and interpolation of research results from animal and patient studies.

Since project grants provide for support not only of research, but also of research facilities—such as research beds or ancillary laboratories—the research portion of the grant is paid from "research grant" funds in the institute appropriation whereas the research facility portion of the grant is paid from "clinical center" funds in the Institute appropriation.

Program accomplishments

Currently, 15 program-projects have been activated in various disorder categories. (Table 6 identifies projects and funds expended.) These include three cerebrovascular research centers at Cornell University, University of Minnesota, and Wayne State University; two epilepsy centers at the University of

Wisconsin and the University of Washington; three neurological clinical research centers at University of California (Los Angeles), Columbia University, and Albert Einstein College of Medicine; a neurosensory center at the State University of Iowa, a sensory disease center focusing on disorders of vision, hearing, and equilibrium at the University of Chicago, and a center to study the connective tissue of the eye as well as connective tissue diseases at the Retina Foundation; a center to study disorders of hearing and equilibrium at Princeton University; a center for investigating disorders of speech and hearing at the Central Institute for the Deaf; a broad basic investigative study of cerebral and related systems, including fine structure modeling of neural networks at the California Institute of Technology; and a study of brain damage and defective brain development in children at Albert Einstein College of Medicine.

TABLE 6.—*NINDB program projects and clinical center grants arranged by disorder category*

	Grants active in 1962					
	Total		Resources		Facilities	
	Number	Amount	Number	Amount	Number	Amount
Neurological disorders:						
A. General.....	4	\$922, 688	4	\$597, 378	4	\$325, 310
B. Chronic neurological disorders of childhood.....	1	220, 886	1	220, 886	-----	-----
C. Cerebrovascular disorders.....	3	660, 440	3	479, 484	3	180, 956
D. Epilepsy and related paroxysmal disorders.....	2	264, 260	2	202, 954	2	61, 306
Sensory and perceptual disorders:						
A. General.....	2	345, 267	2	266, 291	2	78, 976
B. Disorders of vision.....	1	126, 500	1	126, 000	1	500
C. Disorders of hearing.....	1	190, 177	1	187, 677	1	2, 500
D. Disorders of speech.....	1	279, 435	1	254, 435	1	25, 000
Total.....	15	3, 009, 653	15	2, 335, 105	14	674, 548

Two major needs in the development of required additional program-projects for crucial research areas of need, such as cerebrovascular disease, drug evaluation, brain edema, vision and hearing, are adequate numbers of skilled research personnel and sufficient research space. The training grant program of the Institute of Neurology is steadily adding to the pool of trained investigators.

Development of NINDB program projects

Fiscal year	Awards	Operating centers	Center funds
			<i>Thousands</i>
1961.....	6	6	\$996
1962.....	9	9	853
1963, estimated.....	17	16	1, 372
1964, estimated.....	17	17	1, 200

Program highlights

Program projects to date continue to have a strong clinical base. About 40 percent of the funds are for the support of Center facilities. Below are examples of program now underway.

Neurological Clinical Research Center, Columbia University

The goal of the Columbia-Presbyterian Neurological Clinical Research Center is a balanced program of clinical investigation of neurological disorders. During the first year of the grant, progress has been made in the development of laboratories and the investigation of involuntary movements, inherited neurological and muscular diseases, temporal lobe epilepsy, and the pathological physiology of the cerebrospinal fluid. One of the major aims of the program is to encourage residents to participate in research activity.

Studies in progress by members of the pediatric neurology group includes an analysis of cerebrovascular disease in children and chronic anterior horn cell disease in childhood. Studies of both the cerebral and cardiovascular effects of malformations of the vein of Galen and other cerebral arteriovenous malformations have been submitted for publication.

An intensive program of investigation of children with familial dysautonomia has been undertaken in an effort to identify a metabolic basis for the illness. This disorder, with diverse signs of nervous involvement, was first defined at Columbia (Riley-Day syndrome) and many such patients are available for study. The investigation has been directed toward establishing the presence of an abnormal urinary metabolite and finding methods for analyzing urines for phenolic acids and indoles. A group of 15 dysautonomic children and 15 normal controls is under study on an outpatient basis and an inpatient study probably will soon prove essential. When the new laboratories are available, the study will be greatly facilitated. It is believed that the methods now being developed will be useful in the analysis of other metabolic disorders of the nervous system.

Electrophysiological and clinical studies have been carried out in several areas: temporal lobe epilepsy, hemispherectomy for intractable seizures, myoclonus epilepsy, thalamocortical relationships in Parkinsonism, evaluation of new anticonvulsants.

For the past 4 years, serum enzymes in various forms of muscle disease have been assayed and results are in the process of tabulation. Among the data are serial samples from four cases of myoglobinuria. These are of interest not only because this is an uncommon disease, but because of its theoretical implications regarding the source of abnormal serum enzyme activity in muscle disease.

Scientists from several departments have cooperated in completing the study of the original family and the new family with the "Bassen-Kornzweig" syndrome. This is the first of the hereditary ataxias in which there is a clue to the metabolic fault (lack of serum 3-lipo-protein). Other features of the disorder include retinitis pigmentosa, acanthocytosis, steatorrhea, and a complex disorder of lipid metabolism.

Study of unusual patients: Through the cooperation of the Chief of Neurology Service, Veterans' Administration hospital, a study has been made of a patient previously reported as a case of myasthenia gravis with onset after removal of thymoma. The patient now has severe weakness with electrical and histological evidence of polymyositis which does not respond to cholinergic drugs or curare. A case of hyperkalemic periodic paralysis is also currently under study.

Neurological Center for Cerebrovascular Research, Wayne State University

Thirty cases of acute progressive stroke have been treated using the double-blind technique with anticoagulants plus fibrinolysin, or anticoagulants alone. The plan is to complete 50 cases in the study before breaking the seal of the double-blind listing. This should give vital information concerning the use of anticoagulants alone, or anticoagulants plus fibrinolysin, since arteriograms have shown clot lysis in some cases.

Cerebral circulation and metabolic studies have been completed in 98 patients with full arteriographic control. Cerebral metabolic suppression has been demonstrated in acute strokes with lateralization to one hemisphere in some cases.

Sensory Disease Clinical Research Center, University of Chicago

During the last year the otolaryngology service, which has had theoretical priority for 3 beds, has carried out clinical investigations on 3 main types of studies: 24 patients were hospitalized for a total of 404 days.

First, is the use of chemotherapy in the treatment of advanced carcinoma in certain regions of the head and neck. A total of nine patients have been investigated using Methotrexate. Different methods of administration have been used. Results have been encouraging in some cases; there has been decided improvement and at least temporary inhibition of the rate of the growth. A total of 266 days hospitalization were utilized. This study is being continued.

Second is an investigation of special hearing problems. These have been limited mainly to unusual cases which demand further investigation. Eight patients were hospitalized for a total period of 63 days. To date, certain types of congenital deafness have been under investigation. Also, a few patients who

have presented the possibilities for carrying out special tests which may have significance in the diagnosis and localization of central auditory lesions, have been investigated.

The third type of study relates to vertigo and different types have been under investigation. However, only those types which present a diagnostic problem and for which special testing was desirable have been admitted in this category. In all, seven patients were hospitalized for a total of 75 days. These have included postural vertigo of central nervous system origin, postural vertigo and continuous vertigo following stapedectomy, and ultrasonic therapy of the labyrinth.

Since the opening of the ophthalmology unit, 27 patients with a total of 33 different admissions have been hospitalized. These patients were hospitalized for the following studies which have been approved in advance by the Multicategorical Research Center Committee:

- (a) Diurnal tonographic and tonometric studies in open angle glaucoma;
- (b) Study of the immune mechanism in uveitis;
- (c) Etiologic studies of presenile and metabolic cataracts;
- (d) Retinal function in amblyopia exanopsia;
- (e) Percutaneous renal and muscle biopsies in ocular vascular disease;
- (f) Localization of isotopes in intraocular tumors;

Preliminary studies have been carried out in individuals with color vision anomalies.

Three patients with presenile cataracts and no other proven ocular or systemic disease have been thoroughly studied. In addition to the usual laboratory, clinical, and skin test, attention was directed particularly to amino acid chromatography of urine specimens. The findings have been largely negative except for abnormal urine amino acid chromatography patterns in two patients. The abnormalities were not similar and other patients have to be evaluated before the significance of these findings can be evaluated.

Thirty patients have received d,l-iodofluorescein I 125. (Because of the undesirability of administering radioactivity isotopes in a number of hospital areas, these patients were hospitalized in the Argonne Cancer Research Hospital). Eyes containing neoplasms had at least 23 percent more radioactivity after 8 hours than did the other eye. Control eyes, not containing neoplasms, (idiopathic retinal detachment, retinoschisis, benign nevus, macular degeneration, phthisis bulbi, absolute glaucoma) demonstrated less than a 13-percent differential. One false negative was obtained, a patient with a metastatic bronchogenic adenocarcinoma to the choroid; no false positives were seen. However, the total number of patients in this series is small and the percentage accuracy of this technique cannot be reliably ascertained as yet.

Seven patients with myasthenia gravis and one patient with thyrotoxicosis were admitted to continue the investigation of possible endocrine factors influencing this disorder. These revealed the marked beneficial effect on the patient's strength of a rapid infusion of 50 units of regular insulin, together with 40 mEq. KCl in 1,000 cubic centimeters 10 percent dextrose and water. Infusions were run over a period 1 hour with achievement of peak strength at the termination of the infusion, with maintenance for approximately 3 hours. Premedication with anticholinesterase drugs was required in the severe cases of skeletal involvement but not in those cases where involvement was primarily ophthalmoplegic. Administration of KCl in dextrose and water under similar circumstances induced a far less pronounced and shorter lasting improvement. No alteration of serum electrolytes was noted during the test periods.

Epilepsy Research Center, University of Wisconsin

In the first year of the program project in epilepsy, advances were made in the clinical, neurophysiological, neurochemical, and neuropharmacologic areas. These have included observations on the behavioral features of psychomotor seizures, a new method of electroencephalographic study by telemetry, observations on the efficacy of new drugs and observations on psychogenic factors in epilepsy.

In compiling these observations, a total of 66 patients were studied on 83 admissions. Of course, 19 were potential candidates for neurosurgical therapy, and 47 represented challenging problems in drug therapy and evaluation. Only five of the patients in the first group were brought to surgery within the year, due partly to the delay in the remodeling of the research operating room. Thus, only the most pressing of the surgical problems were handled and these were

interesting cases. One of these had a postinfectious cystic lesion of the temporal lobe of some 50 years' duration, and was virtually blind and deaf. The clinical observations of this patient led to studies on the role of environmental clues in psychomotor epilepsy. Another patient, a 17-year-old boy, had a surprising neurocutaneous syndrome with vascular anomalies and a meningioma producing his seizures, and also Parkinsonism.

Drug evaluation studies were extended with six experimental drugs. A publication is in progress describing the effects of Riker 594 in 53 patients.

Observations are beginning to accumulate also on the role of psychogenic factors in epileptics, particularly with reference to the patient who had both bona fide seizures and pseudoseizures on a functional basis.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES .

Program background

Following the 1961 appropriation by Congress of \$500,000 in the NIAID budget for establishment of general clinical research centers, the 1962 appropriations specified that a similar amount should be used by each of the categorical institutes for establishment of categorical clinical research centers.

The Institute was seriously concerned about its responsibilities in developing such centers because of growing appreciation of the probable involvement of disorders of host defense mechanisms in a number of chronic, debilitating human diseases of "unknown" etiology, and the unavailability of counterpart diseases in laboratory animals.

Initial goals

The NIAID is supporting a clinical research center at the University of Colorado Medical Center in the area of allergy and immunology. The center provides for unified interdepartmental clinical research and training in the allied fields of allergy, immunology and infectious diseases.

Presently, the Institute's program objective is to establish additional clinical research centers for infectious diseases, for tropical medicine, and especially for allergy. Four large requests which may qualify for clinical research center support are now in the programming stage. They are in asthma, tuberculosis and the related pathogene, infectious diseases (acute and chronic), and in tropical medicine. Investigations of these potential facilities are being planned. It is anticipated that at least one of these proposals will be reviewed at the March meeting of the National Advisory Allergy and Infectious Diseases Council.

Opportunities are being actively sought in which nuclei of research oriented clinicians associated with academic institutions could be induced to develop additional categorical clinical research centers devoted to these problems.

A system of progressive education and experience is needed to assure that persons are properly trained to become active in the field of basic research in allergy. If the Institute can increase the volume of training in this field, more investigative allergists will be developed.

Current NIAID clinical research centers programs

Since funds have become available for fiscal year 1963, the NIAID staff has undertaken two exploratory visits—one in Denver and a second in New York. The program in Denver will involve a coordinated effort between the University of Colorado Medical Center and the National Jewish Hospital which is engaged in extensive research in respiratory diseases. The program in New York City will probably be headed by a recognized clinician with strong basic research capability. There is a possibility that this program will be initiated as a large programmed project which will develop into a clinical center by fiscal year 1964 or 1965.

The clinical research program at the University of Colorado Medical Center under Dr. David Talmadge is now in its second year of full support. This program has not yet required a separate discrete bed unit for research purposes because of the availability of a general clinical research center, however, the growth of this program will necessitate laying immediate plans for establishing an additional discrete bed unit at the National Jewish Hospital. The strong clinical research orientation in allergy, immunology, and infectious diseases at the University of Colorado Medical Center provides the potential for a highly productive research program in the primary categorical interests of this Institute.

A program project at the Peter Bent Brigham Hospital in Boston for long-term research in tissue transplantation requires studies on both donors and recipients of transplants. Hospitalization for intensive investigations utilizing the present and developing immunologic knowledge for these important lines of research is also carried out. Finally, in the field of allergy, research facilities are being developed at the Kaiser Foundation Hospital in San Francisco (Feingold) for studies on allergic responses to insect bites. It is believed unnecessary to provide extensive clinical bed facilities for such patients; however, it is likely that clinical provisions should be made for a large number of outpatients who could participate in research of this type. An estimated \$100,000 would be required to provide such research facilities.

An important consideration in determining the clinical research needs of this Institute is the provision for clinical services centers and supporting laboratories for outpatient studies. This is particularly true in many of the large-scale studies on allergic disorders. Similar requirements can be identified with parasitic diseases, studies of side and after effects of infectious diseases, and for the study of carrier states in apparently healthy individuals which require clinical service facilities for maintaining a large, continuous long-term research effort with ambulatory patients. Therefore, it is proposed that, in addition to budgeted needs for expanding clinical research activities that require discrete bed units, and in other instances where discrete bed units would not be necessary, funds designated for clinical research centers be identified for these service functions where appropriate. It is felt that a substantial potential for promoting the true categorical interests of this Institute is being delayed and frustrated by the lack of such clinical service facilities for outpatient studies.

Program accomplishments

The research center at the University of Colorado Medical Center has initiated four clinical research projects:

- (a) Organ transplantation.
- (b) Studies of autonomous imbalances in asthmatics using multichannel recordings. An interesting result of this research has established a physiological relationship between adrenaline and histamine on concurrent drug administration. A relationship has long been suspected, but this is the first convincing evidence.
- (c) Studies on clinical cases of generalized vaccinia have been possible. This is a relatively infrequent disease caused by the uncontrolled spread of the vaccine lesion over a large part of the body.
- (d) Studies on staphylococcal infections refractory to antibiotics and a study of new antibiotics is in progress.

The tissue transplantation study at the Peter Bent Brigham Hospital has become established on a program project grant. Funds are to be requested for a discrete bed clinic facility to provide the care and treatment of research patients.

LONG-RANGE COST OF INSTITUTIONAL SUPPORT

In response to the committee's request for cost estimates relating to support of an institutional type, it is evident that needs will increase in absolute terms and as a proportion of the total NIH budget. As a general estimate, a compound growth rate of about 25 percent per year for these programs over the next 5 years is reasonable.

The extent to which this increase will come about as a result of funding through these program activities that would otherwise be financed through other programs cannot be foreseen. For example, further substantial increases in institutional type support will finance activities that would otherwise have been financed through research projects. Accordingly, projected increases in institutional type support cannot be interpreted as requiring a corresponding increase in the total NIH budget.

PRIMATE CENTERS

The use of laboratory primates in research on tuberculosis, poliomyelitis, and neurophysiology has resulted in discoveries of incalculable value to medicine. As a result of these and other research successes as well as the advances in knowledge about animal and human physiology, scientists have increased their reliance upon primates and other animals to support research. Thus, when the Division of Research Facilities and Resources was established at the National

Institutes of Health in July 1962, an Animal Resources Branch was established in the Division to plan and implement a national program for providing animals of the kinds and numbers needed for all areas of specialized medical research. The Primate Research Center program, formerly a responsibility of the National Heart Institute, was transferred to this Branch.

The Primate Research Center program provides research facilities especially designed to house certain species of primates and research laboratories where a resident staff as well as visiting and associate scientists representing many disciplines conduct research to advance knowledge about the biological characteristics of either healthy or diseased primates throughout their entire life span. Of the seven primate centers in this program, one is a national conditioning center and six are regional, the term "region" relating to an integrated scientific community without geographical limitation. The National Conditioning Center is in California; two of the regional centers are on the Pacific coast, one in the Midwest, two in the South, and one on the east coast.

The first primate center award was made in 1960 and the other six by the end of fiscal year 1962. These centers are financed by Public Health Service grants which are awarded to the universities or foundations responsible for the centers' operation and administration.

After an intensive study, the National Advisory Heart Council recommended that primate centers be established to advance research in cardiology. In fiscal year 1960, Congress appropriated \$2 million for the establishment of one or two primate research centers in this country while encouraging further study of the development of a national conditioning center where primates would be studied from capture through the rest of their lifespans.

Eleven applications, totaling more than \$11 million, were reviewed in fiscal year 1960. Of those applying, only one, the Medical Research Foundation of Oregon, Inc., received an award.

In fiscal year 1961 Congress appropriated \$7 million for expanding the program by the establishment and operation of additional primate research centers. Of 16 applications representing more than \$29 million, 3 primate center grants were awarded, 1 to the University of Wisconsin, 1 to the University of Washington, and 1 to Emory University in Georgia.

During fiscal year 1962, Congress appropriated \$9½ million for primate research centers and three center grants were awarded, one to Harvard University, one to Tulane University, and one to the University of California which would serve as a national conditioning center.

Each of these awards provides two grants, one for all construction costs, including acquisition of land, and one for either total or base operating costs for 7 years. The terms of the awards require that the institution receiving the grant serve as a host institution, not only for fiscal management, but also for providing an academic environment of high standard for resident and visiting scientists.

Though each center has its own program orientation, the six regional centers are committed to providing facilities for a broad scope of disciplines using primates in research. The seventh center, a national primate conditioning center, is committed to investigations on the primate itself, including capture and transportation, maintenance under laboratory conditions, and breeding and rearing in captivity. This center will also supply to scientists in regional centers and institutions animals that have unique characteristics and that would be unobtainable from any other source.

There have been many more applications for grants under this program than could be awarded. Each application was reviewed by the Primate Study Section of the National Institutes of Health and by the National Advisory Heart Council. Their recommendations for awards followed intensive reviews of the applications and visits by members of the Study Section and the staff of the applying institutions.

Criteria on which recommendations were based included the scientific caliber of the investigators, their experience in the field of primate research, and the scientific merit of the proposed research to be conducted in the centers. Because the center must be a resource for a community of scientists, the host institution must agree to make the facility and the primates available to visiting scientists and to share information of common interest with other primate centers.

After the awards were granted by the Surgeon General, the institutions began working with their architects and with staff members of what is now the Animal Resources Branch. Because the design of animal facilities is a highly special-

ized field and the design of primate centers a further refinement of that field, architects for all the primate centers have sought guidance from the branch staff, the members of which work closely with the architects throughout the planning and construction.

The conditions of the grants stipulate that, each year, operating costs of the centers are to be negotiated through the Animal Resources Branch staff up to the amount recommended by Council. Additional funds, if needed, are sought through supplemental applications and are subject to Council review. Though the award recommends support for 7 years, the Council periodically will conduct general reviews, at which time, if recommended, additional support up to 7 years is granted. The operational support of these centers may include their total research program.

The present status of each of the primate centers is as follows:

OREGON REGIONAL PRIMATE RESEARCH CENTER

The Public Health Service primate center program was inaugurated in 1960 with the awarding of grants to the Medical Research Foundation of Oregon for construction and operation of a regional primate center. The University of Oregon provides the scientific standards by which the center operates. The new facility, including unique outdoor colony buildings, is on a large tract of land in Beaverton, about 10 miles west of downtown Portland.

The initial research program orientation is on the physiology and biochemistry of the fetus and newborn primates, fetal skeletal biochemistry and growth, congenital anomalies, and cardiovascular physiology and pathology.

REGIONAL PRIMATE RESEARCH CENTER OF THE UNIVERSITY OF WASHINGTON

Grants have been awarded to the University of Washington for the construction and operation of a regional primate research center on the university campus at Seattle. The final construction plans are now in the drafting stage and construction is expected to begin early in 1963.

The center will be a facility for university faculty members using primates in medical, biological, and psychological research and will also emphasize the training of visiting scientists in primate research techniques and primate care. A further, important objective is to serve as a center for disseminating new information about primate research.

Among key investigations to be conducted at the center will be studies in neurophysiology and electrophysiology, gastrointestinal physiology, skeletal and dental development, and obesity and dietary factors in cardiovascular diseases.

WISCONSIN REGIONAL PRIMATE RESEARCH CENTER

Grants have been awarded to the University of Wisconsin for construction and operation of a primate research center adjacent to the present primate laboratory, on a site in the campus extension area. Construction on this facility was begun in October 1962.

Included in this facility will be an area where certain animals will be housed for many years to enable scientists to study them from birth to death, a life span that in rhesus monkeys is sometimes as long as 25 years. An extensive breeding program will be undertaken to provide a constant supply of young animals.

Among investigations to receive special emphasis at this center are studies on biochemical factors associated with mental retardation, postnatal development of the primate brain, hormonal factors in reproductive processes, and variables influencing the development of normal and abnormal behavior.

YERKES REGIONAL PRIMATE RESEARCH CENTER OF EMORY UNIVERSITY

Grants have been awarded to Emory University for construction and operation of a primate research center designed primarily for multidisciplinary study of the chimpanzee. Situated on the university campus, this center will assure the continuation and further development of the psychobiological research of the Yerkes Laboratories of Primate Biology, Inc., owned by Emory University and now situated at Orange Park, Fla. Construction of the new facility is scheduled to begin in the summer of 1963.

Areas of research emphasis of the new center will include studies on the relation of infant growth and experience to behavior in later life; physical, physiological, and psychological attributes of aged primates; brain functions; comparative studies on monkeys and other anthropoids; and effects of unusual environments and intense stimulation.

DELTA REGIONAL PRIMATE RESEARCH CENTER

Grants have been awarded to Tulane University for construction and operation of a primate research center adjacent to Covington, La., about 26 miles from New Orleans. Construction is scheduled to begin late in 1963.

Research emphasis at this center will be on cardiovascular diseases, including experimental, dietary-induced atherosclerosis and hypertension in primates, other metabolic diseases, infectious diseases, radiobiological studies, and behavioral sciences.

NEW ENGLAND REGIONAL PRIMATE RESEARCH CENTER

Grants have been awarded to the Harvard Medical School, acting in behalf of several Greater Boston and New England universities and medical institutions, for construction and operation of a regional primate research center on a 140-acre tract of land in Marlboro and Southboro, Mass. Construction is scheduled to begin late in 1963.

The center will provide facilities and support for (1) investigations in bacteriology, physiology, nutrition, endocrinology, pathology, psychology and behavior in primates; and (2) the acquisition, breeding, and maintenance of a variety of primate species. In addition, the center will train professional and technical personnel in the care and management of primates in research laboratories, and will provide primates that meet special requirements for the research programs of the institutions cooperating in the center program.

NATIONAL PRIMATE CONDITIONING CENTER

Grants have been awarded to the University of California for construction and operation of a National Primate Conditioning Center at the university's campus at Davis, Calif. Construction is scheduled to begin late in 1963.

This center, possibly unique in the world, will serve as a national resource of studies on a wide variety of primates, principal consideration being given to suitable methods of animal transportation, and to ways of keeping primates in normal health as control groups for laboratory experiments. Other studies will focus on the suitability of various species for particular types of biomedical research. Breeding facilities will be developed to provide data on large-scale controlled production. The facilities will also be used for breeding animals of special genetic characteristics. A further activity of the Davis center will be to supply certain animals and animal materials to qualified scientists who require primates with special biological characteristics.

PROJECTIONS

According to present schedules, all seven primate research centers will be in operation by the end of 1964. Once they are in operation, there will be a continuing liaison between the centers and the staff of the Animal Resources Branch. Two major responsibilities in this liaison are the annual negotiations of budgets for operating costs which consider among other factors funds received from other sources for research projects; and a pooling and dissemination of information of common interest to all centers and to the scientific community.

LONG-RANGE COST OF INSTITUTIONAL SUPPORT

In response to the committee's request for cost estimates relating to support of an institutional type, it is evident that needs will increase in absolute terms and as a proportion of the total NIH budget. As a general estimate, a compound growth rate of about 25 percent per year for these programs over the next 5 years is reasonable.

The extent to which this increase will come about as a result of funding through these program activities that would otherwise be financed through other programs cannot be foreseen. For example, further substantial increases in in-

stitutional-type support will finance activities that would otherwise have been financed through research projects. Accordingly, projected increases in institutional-type support cannot be interpreted as requiring a corresponding increase in the total NIH budget.

SPECIAL RESEARCH RESOURCES

BACKGROUND

The NIH special research resources program began with the authorization of \$5 million for computer centers for fiscal year 1962. For fiscal 1963, \$6 million has been made available for the support of a program with somewhat more latitude than the word "centers" implies. Therefore the term "special research resource" has been adopted for a facility providing the basic tools of research and specialized services in support of institutional research programs. Such tools may consist of computers, highly trained technical staff, costly and complex instrumentation, or other aids to a large research operation.

Thus the Public Health Service is financing the acquisition and operation of research resources by research institutions through the Special Research Resources Branch within the Division of Research Facilities and Resources. For example, a clinical research center may support the cost of hospitalizing research patients as well as the operation of related central supporting laboratories and clinics. While such clinical resources, providing central facilities for a number of separate research undertakings, are extremely useful, experience has indicated that other types of central research resources would materially increase research productivity. The Public Health Service is now prepared to consider applications to support resources for facilitating research in the areas listed below.

Project grants supporting special research resources will provide specialized or unusual services required for research in medical and related sciences, including instrument and electronic development, computing and data processing, and bioengineering. Needs for other types of special research resources will be considered by the Public Health Service with a view to determining whether support for them should be provided.

Special research resources will generally provide research services to several lines of research in one institution, which may be a university, medical school, or other life science-oriented research organization. For example, a computer research resource will provide the technical staff and expensive hardware to conduct computations for many health-related research projects within an institution. At the same time, it will provide facilities for the conduct of research involving statistical methodology and applications of mathematics to research in the life sciences.

The resources will be typically staffed by personnel with diverse backgrounds and training, but with a common interest (such as computer technology, biomedical engineering, instrumentation). On-the-job technical training will be provided in the resource to the fullest extent compatible with institutional policy and fulfillment of the primary research function. Senior investigators using the facility will be encouraged to apply through established NIH programs for support of graduate student training at the facility.

Special research resources should meet a clearly defined institutional need, and should be an integral part of the general plan of development of the applying institution. The Public Health Service supports special research resources as a program designed to expand in a rational and effective way the total research capability of the Nation.

Special research resources must be associated with institutions which possess extensive research programs of high quality, together with a staff with the competence, interest, and desire to make proper use of the resources in their respective investigations. Although a special research resource may facilitate research already supported by NIH, it will provide neither for research nor training support which can be obtained through the usual NIH programs.

In addition to computer resources work now is in progress toward establishment of special research resources in biomedical engineering which will draw upon the life sciences, engineering, the physical sciences, and mathematics to develop new technologies and theories in which physical and engineering principles are applied to biological and medical problems. Research supported by

such a biomedical engineering special research resource can provide instrumentation for monitoring bodily functions; for the development of new prosthetic devices for the deaf, the lame, and the blind; and for the formulation of new theories of cell and organ activity. It is apparent that such resources will necessarily involve much expensive equipment and shop facilities, as well as a core of highly trained engineers, mathematicians, and life scientists.

Medical science can profit by concentrating a variety of interrelated techniques on a basic problem. There are obvious advantages to an attack upon the structure of proteins in living cells using such physical methods as X-ray crystallography, ultrasound, and other highly sophisticated physical techniques in combination with skilled biochemical technology. A resource in physical biology could provide the highly trained technical staff as well as sophisticated and costly apparatus for supported research in this field.

ACCOMPLISHMENT

On October 1, 1962, 18 approved programs (now all activated) were transferred from the Division of General Medical Sciences to the Division of Research Facilities and Resources. These programs included 17 computer centers and one biomedical engineering facility.

Reviewed at the November 1962 meeting of the National Advisory Health Council were 15 applications: 13 for computers, 1 in biomedical engineering, and 1 in the biomedical information field. Of these, five were approved and one was deferred pending a future site visit.

The program now concentrates largely in development of computer technology and computer usage for health-oriented research activities. One program has been financed in the area of biomedical engineering. The emphasis on computers has occurred largely because of the activities of the Advisory Committee on Computer Research resulting in heavy programing in computer usage. The Special Research Resources Branch encourages those types of centers which will aid, totally, institutions or regions to advance or improve their research capability in the health-related sciences, thus contributing powerfully to a multicategorical attack on the dread diseases.

Active special research resource centers

Type	Number	Funds expended prior to fiscal year 1963	Funds expended in fiscal year 1963
Computer.....	17	\$4, 485, 720	\$1, 958, 229
Biomedical engineering.....	1		287, 160
Total.....	18	4, 485, 720	2, 245, 389

SCIENTIFIC HIGHLIGHTS

Many biologists today are engaged in investigations associated with information-processing capabilities of the biosystem through the use of computers. An exceedingly strong case can be made to support the view that one of the most challenging frontiers of science lies within this area of interest. Although a great effort is being made in this country to bring conventional mathematical and statistical techniques to bear on biological problems, there is a smaller but significant group of talented biologists who possess highly sophisticated skills in mathematics, computer technology, and simulation. These latter scientists work largely in the field of biophysics and neurophysiology. Important accomplishments by this group include recent advances in: the concept of the transmission of nerve impulses; study of the electrocardiogram; and analysis of bioelectrical signals. These advances result in new knowledge of the nervous system and may lead to breakthroughs in mental health, polio, and nervous diseases.

Other areas of research include: the transmission of pressure waves by arteries; the control of circulation during exercise; descriptions of the dynamic characteristics of blood pressure control; and control of heart rate, leading to new knowledge to be applied in heart disease, atherosclerosis, and stroke.

Still other important contributions through computer-assisted biological studies are: the development of the concept of the control of respiration; the development of a model of rhythmic activity in nerve nets; the distributions of mechanisms of conduction in heart muscle; studies of the X-ray crystallography of myoglobin (the form of hemoglobin found in muscle fibers); and development of a series of computer programs for complex statistical analysis of biological data.

The ever-increasing interest in and exploration of neuroelectric activity have already had an impact on computer design. The recently developed laboratory instrument computer (LINC) by Wesley Clark of Lincoln Laboratory was clearly a response to the need for a machine capable of accepting analog input, converting this to digital form, evaluating and displaying the output in different ways. While in the last analysis a linc computer is a very modest machine, containing elements already well within the state of the art, its use in the laboratories of physicists and physiologists will shortly create a demand for a much increased capability. When this point is reached, demands may be made of the computer engineer which cannot be resolved by techniques within the present state of his art. It is quite possible therefore, that developments in memory and logic will lean heavily on the experiences of neuroelectric and neurochemical biology.

Other special research resources may be developed in the near future. The problem of communications within the scientific community demands an attack upon the fundamentals of data acquisition and retrieval, communications methods, and a study of communication theory. One of the program objectives of the Branch is the development of basic programs in this area.

The scientist is often confronted by the problem of determining the instrument to be used in measuring a given physiological or biochemical parameter. The development of new forms of energy transducers together with the accessory apparatus to make finer or more accurate measurements as well as the monitoring of bodily activity by "electronic pills" combined with using advanced techniques in telemetry, requires the formation and staffing of special instrumentation facilities where such equipment can be designed, built, and tested by qualified life scientists and engineers.

Expansion will occur as a result of several factors: not only by the formation of new medical schools and new graduate schools which will produce a rapid growth in biomedical research productivity to be met by increased need for facilities for research, but by the current strong research program in computers, biomedical engineering, and communications. Although only one such program in biomedical engineering has been founded to date, many inquiries have been received. The estimates which are provided are based on applications received and on inquiries to Branch staff members.

It may be anticipated that growth of the special research resources program will be more rapid than the projections for NIH as a whole. The tendency toward large-scale projects, the need for increasing the funds necessary to support individual workers, the increasing cost of complex apparatus, greater emphasis on long-term studies and the necessity for higher paid skilled technical supporting staffs—all tend to make a special resource facility the most satisfactory method for providing research support to a variety of large programs within a given institution or region.

Projections for health communications are based on estimates of the need rather than on programs in operation. One program is now under consideration which will approximate \$1 million over the next 5 years. As new methods develop for retrieval of information, for design of new types of computer for semantic purposes, and as the flood of scientific information increases, placing greater demands on conventional methods, it is anticipated that a progressively greater increase in funds for this activity will be necessary. For example, it is not beyond the realm of possibility for a computer designed along new lines of logic with a new and larger memory, to cost several million dollars.

LONG-RANGE COST OF INSTITUTIONAL SUPPORT

In response to the committee's request for cost estimates relating to an institutional-type support, it is evident that needs will increase in absolute terms and as a proportion of the total NIH budget. As a general estimate, a compound growth rate of about 25 percent per year for these programs over the next 5 years is reasonable.

The extent to which this increase will come about as a result of funding through these program activities that would otherwise be financed through other programs cannot be foreseen. For example, further substantial increases in institutional-type support will finance activities that would otherwise have been financed through research projects. Accordingly, projected increases in institutional-type support cannot be interpreted as requiring a corresponding increase in the total NIH budget.

RESEARCH CAREER PROGRAM

The research career program is meeting an urgent need hitherto met inadequately in research institutions. This need is the provision of assured salary support on a long-term basis for scientists who can demonstrate their research excellence in national competition.

The program consists of two types of awards. The first is for younger investigators who show clear promise of developing into investigators of stature. These awards are limited to 5 years, with one renewal of a maximum of 5 years in unusual circumstances. The second type of award is literally for career support. The Public Health Service commits itself to provide the total salary support of carefully selected investigators for the duration of their careers. In return, those who are selected obligate themselves to devote their efforts totally to research, teaching, and associated academic activities. The obligation is, in fact, an opportunity.

On the part of some universities, unfamiliarity with such a form of support, and concern over the policy implications of having the Federal Government pay the total salary of faculty members with tenure, gave rise to some hesitation in applying for awards. On the part of the National Institutes of Health, time was required to resolve some complex problems that arose despite the essential simplicity of the idea. Both sets of problems have been resolved, essentially by clarifying the minimum essential conditions required on the part of the Government for an award, and by emphasizing that once an award is made and the minimum conditions accepted, the awardee is a faculty member with all of the obligations and rights associated therewith.

The awards made at both levels are consistent with the salaries paid to persons with comparable academic rank and attainments. The average annual award to those at the developmental level is \$12,500; the average for those at the career level is \$18,300. A ceiling of \$25,000 per year for salary payments is set, and only 9 percent of the awardees have been given awards at the maximum level.

The awards at both levels are expanding substantially the number of faculty members who devote their full time to research, teaching, and directly related activities. One effect of the program which has been more pronounced than was anticipated has been to relieve a substantial number of senior faculty members of the need to practice medicine to produce income for themselves or for their institutions. At the lower faculty levels, the major effect of the program has been to substitute assured long-term support for the short-term support available as salary payments from research grants.

In terms of numbers of awards, the budgeted positions under this program have increased from 630 in fiscal year 1962, to 1,077 in fiscal year 1963, to 1,130 proposed in the President's budget for fiscal year 1964. The program is well launched toward the objective of providing a solid underpinning of stable support for full careers devoted to investigation in medicine and allied fields.

GENERAL RESEARCH SUPPORT GRANTS

BACKGROUND

The tremendous surge of support for medical research following the last war has contributed to an extraordinary increase in new scientific information; it has also generated some problems. In May 1960, a Committee of Consultants on Medical Research said: "The support of investigators by a Federal agency on an individual project basis, after review and approval by committees of experts, has been outstandingly successful and has been carried out with great wisdom and flexibility. This support, however, comes to the schools and research institutions through requests of individual investigators without regard for the overall plans

of the institution and with conditions attached which may not fit into its program. This can lead to an uneven development which may not be in the best interests of the institution as a whole."¹

The committee recommended that the Public Health Service be permitted by law to make "institutional" grants, upon recommendation of an appropriate council of the National Institutes of Health, to public or nonprofit universities, hospitals, laboratories, research institutes and other institutions, for the general support of their health-related research and research training programs.

In September 1960, Congress amended the Public Health Service Act, authorizing the Surgeon General, upon recommendation of the National Advisory Health Council, to grant funds to eligible institutions for the general support of their research and research training programs. An amount up to 15 percent, as determined by the Surgeon General, of funds provided through NIH appropriations for research projects for any fiscal year may be transferred from such appropriations to a separate account available for research and research training activities under the general research support program.

General research support grants enable institutions to capitalize on emerging opportunities in research, to explore new and unorthodox ideas, and to use the funds for the stimulation and development of their overall research program, including research training. This type of broad support is designed to give institutions better balance in their total research programs and to strengthen their exercise of scientific responsibilities for administration of these programs under conditions and in directions of their own choice.

Originally administered by the Division of General Medical Sciences, the general research support program is now administered by a branch of the Division of Research Facilities and Resources established at the National Institutes of Health in July 1962.

OBJECTIVES

The first awards of the program were made in January 1962. In its first year, the program was limited to schools of medicine, dentistry, osteopathy, and public health, and it awarded a total of \$20 million to 86 medical schools, 49 dental schools, 12 public health schools, and 6 schools of osteopathy.

Approximately 5 percent of NIH appropriations for research projects was made available for the general research support program in fiscal year 1962. In fiscal year 1963, \$30 million, representing about half (approximately 7 percent) of the total amount allowed by the law, has been designated for the general research support grants program. This increase of \$10 million over the amount available in fiscal year 1962 permitted the extension of support to schools of pharmacy, nursing, and veterinary medicine, as well as research institutes, centers, certain laboratories, and other nonprofit organizations heavily engaged in health-related research.

The awards made through this program represent a percentage of the amount of Federal research project grants and contracts awarded to the institution, plus a somewhat larger percentage of the institution's budgeted research funds from non-Federal sources. The greater weight assigned to this latter factor is intended to provide an incentive for institutions to seek non-Federal funds.

The method of relating the amounts of general research support to the amounts of an institution's research project grants and contracts fulfills the intent of the law by helping institutions develop well-balanced research and research training programs.

Evaluation of progress reports due in the early part of 1963 will furnish useful information about the use of general research support funds and guidelines for future operation of the program.

ACCOMPLISHMENTS

Though the formal progress reports have not yet been received, program information obtained through visits to institutions, from correspondence and other informal channels, indicates conclusively that institutions receiving these funds are already reaping benefits in many ways. Some, for instance, are upgrading and strengthening departments which previously were unable to attract senior staff. As a consequence, these institutions have been able to meet criteria for

¹ Report of the Committee of Consultants on Medical Research of the Subcommittee on Departments of Labor, and Health, Education, and Welfare of the Committee on Appropriations, U.S. Senate, 86th Cong., 2d sess., May 1960.

other research and research training grant funds for which they were not eligible in the past.

Some examples of accomplishments during the first year of the program are:

One school established and staffed a new experimental endocrinology laboratory. Within the next year or so, salaries paid from the grant will be picked up by the university budget, thus releasing the general research support grants funds for development of other research activities. This school also provided and staffed a new animal surgery for research. A health physicist was brought on the staff and supported in radiation safety and research. An instrument development shop was established for the research support of several basic science departments. The school has undertaken a pilot study on the breeding of animals for research. The funds have also provided support for several students at the postsophomore level in beginning their research training.

Another school was able to appoint three research professors, one in anatomy, one in biophysics, and one in human genetics. A fourth professor will join the staff in the department of medicine next year. This school also increased the research potential of several able, permanent members of the faculty by putting them on a 12 months' salary instead of the usual 9. The institutional research training program has been expanded and can now invite interested, qualified college and "quarter off" medical students to participate in research training.

A third school established three new divisions of wholly independent research activities, i.e., a division of molecular biology in the department of biochemistry; a division of neurophysiology, a joint endeavor between the departments of physiology and neurology; and a division of genetics in the department of microbiology. Senior research people have been recruited and others are being sought. Basic salaries for professionals and for the costs of initial equipment have been supported by the grant.

Another school reports that 80 percent of the general research grants funds were used in basic research and approximately 20 percent in research training. According to the dean, the grant has enabled the school to do a number of things important to the development of long-range capabilities. For example, they were able to establish an electron microscopy unit and to set up and staff a tissue culture laboratory in anatomy. In addition, research activities were supported in the departments of physical medicine, otolaryngology, dermatology, and surgery. Some excellent pioneering and exploratory studies in basic research have been initiated.

PROJECTIONS

A. Institutions currently eligible

In order to support those institutions currently eligible \$75.8 million per year will be required by 1968.

B. New medical schools

At present, about a dozen new medical schools are being planned or are in the early stages of development. According to the Bayne-Jones report² some 20 new medical schools will be needed by 1970. The general research support grants program can be of inestimable benefit to these new schools, enabling them to develop during their early stages a broad base of the highest quality research and research training.

Because many of these schools are in various stages of development any estimate of support for them must, of necessity, be tentative at this time. It is estimated that a total of \$1.3 million will be needed for general research support grants for five new medical schools by 1968.

C. Special grants

To realize its purpose of fostering high-quality research and research training, NIH should support these endeavors in all health-related areas wherever they may be. The direction and the emphasis of the research itself can best be determined by topflight scientists permanently and adequately supported in their efforts to discover, evaluate, and pursue promising leads. Such endeavor demands inte-

² The advancement of medical research and education through the Department of Health, Education, and Welfare: Final Report of the Secretary's Consultants on Medical Research and Education, July 27, 1958.

grated, balanced research approaches possible only by uninhibited cooperation among all basic health sciences—physical, social, and biological.

To aid in creating this highly desirable research atmosphere, it is imperative to award a series of grants to carefully selected institutions which have the appropriate facilities and scientific competency.

In 1964 it is planned to award a series of grants to five such competitively selected institutions for a period of 5 to 7 years, followed by awards to an equal number of institutions in each of the following two fiscal periods. This program will require about \$5 million the first year and a total of \$30.5 million by 1967. Increases beyond 1967 will be determined after comprehensive evaluation of the scientific merit of these programs to ascertain their contribution to the development of the best long-range growth in research excellence.

LONG-RANGE COST OF INSTITUTIONAL SUPPORT

In response to the Committee's request for cost estimates relating to support of an institutional type, it is evident that needs will increase in absolute terms and as a proportion of the total NIH budget. As a general estimate, a compound growth rate of about 25 percent per year for these programs over the next 5 years is reasonable.

The extent to which this increase will come about as a result of funding through these program activities that would otherwise be financed through other programs cannot be foreseen. For example, further substantial increases in institutional type support will finance activities that would otherwise have been financed through research projects. Accordingly, projected increases in institutional type support cannot be interpreted as requiring a corresponding increase in the total NIH budget.

GENERAL CLINICAL RESEARCH CENTERS

MR. FOGARTY. Now would you take each of these programs and summarize the results of the analysis? Tell us how they should be developed in the future if you think they should and what development is planned under this budget.

I think we should start with the clinical research center program; then go to the primate centers; then the special resource centers; and the general research support grants.

DR. SHANNON. Mr. Chairman, these are all Dr. Stone's area of administrative responsibility.

MR. FOGARTY. All right, Doctor.

DR. STONE. At the present time, the general clinical research center program is supporting about 60 centers.

These centers, actually, produce two remarkable effects.

Because of the provision of excellent clinical research facilities within the centers, they are able to provide for a great increase in clinical research, which is their primary intent. However, secondarily, and perhaps equally as important, is the impact of these centers upon their institutions, as follows:

IMPACT OF CENTERS ON THEIR PARENT INSTITUTIONS

These centers have provided a hitherto unavailable opportunity for clinicians, who have been doing nonclinical laboratory research, appropriately to bring their nonclinical research to the bedside.

They provide additional resources, which have effects upon the institution in ways that were not predicted.

They have helped the boards of trustees, the auxiliary staff, and the public, to realize what first-class clinical research really means in a unit dedicated to that particular activity.

In addition, they have provided a focus within the institution, where research which otherwise has been supported by many agencies, comes together in one unit. In one center which we have investigated, we have found during the last complete year of operation that about 30 additional clinical research investigations have gone on, most of which would probably not have been undertaken, without the center and its supportive stimulation.

These investigations are varied, but they are carried on, each one in depth. In this particular center there were, I believe, eight different funding agencies, whose research was being carried out in this center. They were, for instance, both public and private agencies—private agencies, such as the American Heart Association; the American Cancer Society; the Muscular Dystrophy Association; as well as four Institutes of National Institutes of Health and even the Department of Agriculture, in this particular case.

This is an advanced center unit—one of those that was set up very early in the program. The program of general clinical centers is less than 3 years old, and we expect that this history will be repeated in other centers as they come to maturity.

PLANS FOR THE FUTURE

As to our plans for the future, we do plan a modest increase in the numbers of these centers. The committee may wish to know that these centers are given the same kind of review, intensive, scientific, review in depth, which is common to the other programs in NIH, and which was discussed at length yesterday by Dr. Shannon.

We do not anticipate any markedly different kinds of centers in the ensuing fiscal year but a modest increase in number.

The next item that you asked me to discuss was the primate centers, sir.

Mr. FOGARTY. That is right.

PRIMATE CENTERS

Dr. STONE. The primate center was originally started by the National Heart Institute upon the recommendation of the National Advisory Heart Council and will be transferred to the Division of Research Facilities and Resources as of July 1 of this year. This has been a program which has been planned over a 3-year period and now results in seven discrete regionally located primate centers.

These centers have been slow in building, if judged by other programs at the National Institutes of Health, and the reasons have been the need for extensive prior planning and the requirements for special construction, which is necessary for these centers. Also, the land had to be purchased close to the university but isolated enough to be suitable. The development of scientific programs in each of these centers will show a capability to pursue research wide in scope and of long-term nature upon subhuman primates.

All of the centers are in active building stages or have been completed. It is not intended at this time to extend the program to additional regional centers during the next fiscal year. We prefer to study their development at the moment.

HISTORICAL BACKGROUND

Dr. SHANNON. I would say, Mr. Chairman, you might be interested in some of the historical background of the center. The initial recommendation by the National Advisory Heart Council some years ago was to establish a single national center for this activity. This recommendation came to Dr. Terry and in parallel with that recommendation our advice to Dr. Terry was that the need for primate facilities was great but that we felt the needs of science across the country would not be satisfied by a single center that was multipurpose in design, but rather, we suggested that a very serious study be made with the end in view of seeing if a limited number of specialized centers would fit the general need. We felt that putting the management of these centers in the hands of the universities rather than attempting to run it as a Federal operation would assure continuity of purpose and a high professional conduct of these programs and would make the resources more generally available to the scientific world.

It was on this basis that we came in for a request of \$3 million for the initial year. Now, as Dr. Stone has said, it was apparent very early that we were getting into an area of science support which is very important to the progress of science, but in which we have had little experience. Therefore we felt that this initial group of centers should be established and then the total group should be watched very carefully for several years before any attempt was made to assess the total need and determine whether in fact we had satisfied it.

PLANS FOR THE FUTURE

We feel that quite likely some 2, 3, or 4 years hence we may come back for the establishment of another one or two. We feel that with the present order of magnitude and the present level of diversification, we now must obtain some broad operating experience with the centers before the program is considered for further expansion. I might say, as happens not infrequently in the area of science where resources usually follow need, that during the period of development of this program it has turned out that the Heart Council was very farsighted in its appraisal of the situation, because now during the close of this period of development of the program itself, the need and opportunity has expanded tremendously as compared to what it was during the initial period of the program development. I have no doubt at the present time that these centers will be a very important addition to the capabilities of our scientists.

I think what they will show, on the other hand, is to point up something of a general operating principle which we have been considering for some time, but upon which we are quite unwilling to make any recommendation now. We may well address ourselves to the establishment of other animal resources in years to come and attempt to handle these on a comparable basis as an integrated, centralized operation.

The Cancer Institute requires fairly large quantities of purebred strains of mice and rats—they need specialized production of genetically stable hamsters and a wide variety of specialized animals. It seems that this need will emerge as time goes on as one of the most important research resources that will be required, and it was in

appreciation of the fact that science had attained the complexity where certain resources had to be furnished on a national basis, rather than on an institutional basis, that led us to establish this new division as the focal point within NIH that will be responsible for the continual assessment of the national need for this type of research responsibility.

GENERAL RESEARCH SUPPORT GRANTS

Dr. STONE. I will go on to general research support grants.

The general research support grant program is in the second full year of its operation and was funded this year at a level of \$30 million. The committee will recall that this was a program designed to give general support to research and research training in institutions that have already demonstrated that they are heavily engaged in research. Such institutions were initially chosen to be the schools of medicine, dentistry, osteopathy, and public health. There has subsequently been added additional research institutions such as veterinary medicine, research institutes, hospitals, and so forth.

FLEXIBLE RESEARCH SUPPORT

The program so far, we are convinced, shows the fundamental wisdom of its propounders in that it has provided flexible funds to the schools of the health professions in our universities and to the separate research institute hospitals which these recipient institutions may use to develop new or unorthodox scientific advances upon certain problems. They have permitted the schools to stabilize salaries so that the drainoff of the highly gifted scientists to other activities is not so great as it once was. These men and women are not forced to go into private practice, for instance. It has permitted the institutions receiving these funds to set up permanent positions in different categories that do not easily integrate into the formal medical school structure.

The program, although a new one, has demonstrated fully the wisdom of the original guidelines which were put into effect. It also permits the institutions to exert their own initiative primarily to decide what their programs will be, which are of very particular concern to the institutions themselves. Only after programs of research have matured do they then need to go into national competition for national support from any of the public and private agencies, thus releasing funds back to the institution with which they may start other enterprises of interest to them. It permits the institutions to maintain a research balance in accordance with the institutions' own plans.

Dr. Shannon has discussed just before I came on, in his prepared statement, the program of a very few model centers for the health research sciences involving in novel ways the medical schools and the so-called university sciences. This is a program which we have under study at the moment. It is not proposed specifically as a program advance in the on-coming year. We have at the moment about 300 health research institutions receiving the moneys available in this fiscal year.

Now sir, I will conclude with a reference to our special research resource program, of which biomedical engineering centers are a part.

These resource centers as currently planned are to provide massive highly specialized resources centralized within an academic institution, the major purpose for which is to make available to the host institution and to other institutions within the immediate geographical region a research and research training capability of a markedly increased order of effectiveness and productivity. A few examples of our present centers meeting the above criteria are those involving electronic computer and data processing centers and biomedical engineering and instrumentation centers. The latter type of center has just previously been mentioned.

At the present time we are giving serious study to the possibility of funding special resource centers in order to assure adequate production under controlled conditions of pure lines of mammalian cells in large quantities and centers for the large-scale production of enzymes, selected proteins, and special subcellular components. Initial evidence in our hands strongly indicates that these two additional types of centers, when under full production, would provide scores of investigators with much needed material of a biological and chemical nature which they do not now have in adequate amounts or in adequate purity.

INTERNATIONAL CENTERS FOR RESEARCH AND TRAINING

Mr. FOGARTY. The International Centers for Research and Training are also institution oriented, are they not?

Dr. CUMMINGS. Yes, sir. They are truly multicategorical centers in the sense that each American university which has a domestic base linked to a foreign base concerns itself with research of interest to many NIH institutes.

LOCATION OF CENTERS

Mr. FOGARTY. There are not many. How many are there?

Dr. CUMMINGS. There are five on-going programs, Mr. Chairman.

The first links the University of Maryland with the University of Lahore in Pakistan. The second links Johns Hopkins University, both the School of Medicine and the School of Public Health with the Calcutta School of Tropical Medicine. The third links the University of California with the Institute for Medical Research in Malaya. The fourth links Louisiana State University with the new University Medical School in San Jose, Costa Rica, and the fifth brings together Tulane University with the University del Valle in Cali, Colombia. The principal purpose of those programs, as Dr. Shannon defined it in past testimony, is to provide an offshore base for research training of Americans. They are not principally designed to upgrade or develop the host nation. Nevertheless, I think such a secondary effect will occur, since foreign scientists join with our American scientists in the studies of the problems of mutual interest and concern.

Mr. FOGARTY. You do not have any school here working with a school in Israel?

Dr. CUMMINGS. No, sir; there is no formal linkage with either the Weitzmann Institute or the Hebrew University Medical School, al-

though we do have in our Public Law 480 programs a number of collaborative studies which I will discuss with the committee at a later time during these hearings.

Mr. FOGARTY. How are these centers working out? Are these centers really producing now?

Dr. CUMMINGS. Yes, sir; I am pleased to report this year that all of the international centers have developed vigorous research and training activities. You will recall in our conversations last year we could only report that they were staffing up and tooling up for the operation. The special advisory committee which carefully reviews these particular programs has recently completed a series of visits to the domestic and foreign bases and reports to us that in each institution a very dynamic program is on-going.

Mr. FOGARTY. Doctor, of these five, will you briefly explain the programs covered by each and put a more detailed statement in the record?

Dr. CUMMINGS. The general pattern of research and training in the five centers is usually built on the unusual or unique opportunity which exists in the five foreign settings. Thus, for example, in Malaya, the principal theme of the research program is studies of human disease as they may relate to the local ecology, be it animal vectors or disease or influences of other environmental and social factors. In the programs in India, where infectious diseases are rampant and incidentally, where some of the infectious diseases may have effects upon American residents in the area, or passing through the area, the Johns Hopkins team has addressed itself to studies of problems such as cholera, severe enteric diseases, diarrheas, particularly parasitological diseases that occur in abundance in these areas.

I would be very pleased to put in the record a more comprehensive statement.

(The statement follows:)

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

The University of California (San Francisco) with the participation of the Hooper Foundation, the school of public health, and the medical school, is collaborating with the Institute for Medical Research, Kuala Lumpur, Malaya. This International Center has placed strong emphasis on infectious diseases transmitted from animals to man. Because of this longstanding research interest and experience at the University of California a collaborative program embracing medical zoology, microbiology, and parasitology has been developed to study fundamental problems of human ecology. The scope of this collaborative endeavor has now been expanded to include related sociocultural research and medical genetics.

Studies now in progress on the University of California campus include investigation of arthropod-borne viruses and methods for their rapid detection and isolation, studies in bilirubin metabolism, investigation of snails and other mollusks as intermediate hosts of parasites important to man, and the development of improved field survey techniques related to the incidence of coronary heart disease and the influence of diet in its pathogenesis. A comparison study of coronary disease among Malays and Chinese will be initiated in Malaya in the summer of 1963. Studies now in progress in Kuala Lumpur seek to clarify the relationship of primate (monkey) to human malarial infection. Virus research in the foreign affiliate is concerned primarily with the relationship of dengue virus to hemorrhagic fever. Sociocultural studies concerned with Malayan attitudes toward health and nutrition and the influence of native and Western practitioners of medicine upon these attitudes are now in progress under the direction of a social anthropologist.

Johns Hopkins University (Baltimore) with the participation of the school of hygiene and public health and the department of medicine is collaborating with the Calcutta School of Tropical Medicine, the All-India Institute of Hygiene and

Public Health and the postgraduate institute for medical education and research in Calcutta, India. Program emphasis in this institution is directed toward the training of scientists for the study of disease in tropical areas, especially the study of disease as it occurs in large population groups. The Johns Hopkins staff is conducting intensive biochemical studies in cholera, a devastating disease accompanied by sudden dehydration of the body. Research in this disease is yielding considerable knowledge of kidney function and the most effective methods for combating dehydration induced by this and other bacterial infections.

The location of this research unit lends itself uniquely to the study of smallpox which is endemic in this area. Therapeutic trials of drugs believed to be effective in the treatment of smallpox are now being initiated. The discovery of such drugs is of vital importance not only for the treatment of smallpox, but for the entire spectrum of human viral disease.

In addition, comparative studies are now underway in India on some chronic diseases which are of significance to the United States. These include an investigation of the high incidence of cirrhosis of the liver which occurs in Indian children and young adults in the absence of alcohol ingestion or exposure to other toxic substances frequently associated with this condition.

Louisiana State University (New Orleans) with the participation of the School of Medicine, is collaborating with the University of Costa Rica in San Jose. The location of this research center provides an exceptional opportunity for the meticulous study of cancer of the stomach which is extremely prevalent in Costa Rica. A current statistical survey of the problem and extensive pathological studies are being conducted to compare this disease with that observed in the United States. Conversely, the low incidence of cancer of the lung in this geographic area provides an interesting opportunity to study the possible relationship of smoking habits to the development of pulmonary malignancy as contrasted to findings being reported in the United States.

A prospective study of diarrheal diseases among 300 families in this community is being conducted to provide basic epidemiologic data for these diseases which constitute a major cause of death in all age groups in Costa Rica.

A similar prospective study of amebic dysentery is now being carried on through the collaborative efforts of a parasitologist, bacteriologist, virologist, pathologist, epidemiologist, and a clinician. In the course of this survey some of the basic problems of *Entamoeba histolytica* parasitism will be reexamined. New approaches to the problem of control of intestinal parasites are being considered by members of this staff to discover means by which hookworm anemia may be more satisfactorily treated. Studies of this type are providing for the first time fundamental knowledge concerning individual patient response to amebic dysentery and varying degrees of immunity which may develop against this infection.

Tulane University (New Orleans) with the participation of the departments of tropical medicine and public health, other departments of the medical school and the department of anthropology and sociology is collaborating with the University del Valle, Cali, Colombia. The program in this South American center is directed toward the epidemiologic study of diseases of mutual interest to the United States and Colombia. Among these is a longitudinal survey of diarrheal diseases of infants and young children. Although nutritional, environmental, and chemical factors may be associated with this symptom complex, studies are now underway to discover the extent to which bacteria, viruses, or parasites are involved in these debilitating diseases of early life.

Another investigation in experimental epidemiology relates to the frequent occurrence in Colombia of tetanus (lockjaw) in newborn children and its effective prevention through the use of tetanus toxoid administered to women during pregnancy. This study is expected to yield fundamental immunologic information on the quality of toxoid-induced protection against this disease and the duration of such active immunity produced in human beings.

The Tulane staff is further investigating the ecology of Colombian disease employing the technique of correlation maps to discover those biological and environmental factors which contribute to the geographical distribution of human disease.

To explore the cause of the unusually high incidence of gallstones and gall bladder disease in this region, medical and surgical studies are being conducted in Cali to further clarify the pathologic features of extrahepatic biliary disease and the excretion of certain dyes by the liver in these conditions.

University of Maryland (Baltimore) with the participation of its School of Medicine, and collaborating with the Institute of Hygiene, Lahore, has initiated

an extensive research program in west Pakistan. This includes studies of mosquito-borne viruses in man, the role of mosquitoes and ticks as vectors in human disease, identification of vertebrate hosts in the transmission of scrub typhus, an evaluative study of penicillin in the treatment of typhoid fever, and an investigation of specific nutritional problems among Pakistani children. A comprehensive survey of the causes of enteritis in the Lahore area of Pakistan is now in progress. In addition, a detailed investigation of tuberculosis-like bacteria which cause lung disease in humans is now underway. The use of drugs such as isoniazid in mass prophylaxis against this unusual pulmonary disease is now contemplated.

Comprehensive studies of arthropod-borne diseases have been set up, as well as research in the rickettsial diseases which are endemic in this area. Recent evidence indicates that mites, present on wild rodents, are important agents in the transmission of typhus. The geographic and seasonal contribution of scrub typhus is now being investigated in a systematic fashion as well.

Nutritional studies developed by the department of pediatrics are in progress at the oversea affiliate. These include simple, inexpensive techniques for mass screening for defects in nutrition. In addition, growth data and X-rays are being utilized as an index of the state of general nutrition in a well-defined population of Pakistani children. The interrelationship of nutritional defects and microbial disease is one of the ultimate objectives of the present investigation.

BUDGET REDUCTION FOR INTERNATIONAL CENTERS

Mr. FOGARTY. Why do you plan to reduce support for the international centers from \$3,692,000 in 1963 to \$3 million in 1964?

Dr. CUMMINGS. Quite frankly, we did not plan this reduction, but felt with the orderly buildup, which does require at least a year's leadtime, that we could maintain the level of the operation with this particular budget. The advisory committee which has reviewed the program has had interest not only in expanding the depth and breadth of the operation professionally, but has felt from time to time that we should attempt to establish one additional center in Africa, south of the Sahara.

I should tell this committee, however, that as of this moment, we have been unable to identify the strong university linkage required to make this a successful operation, so that in part, the reduction you refer to is related to our current belief that Africa—an African center—will probably be postponed for another year.

Mr. FOGARTY. Is the advisory committee happy with \$3 million for 1964?

Dr. CUMMINGS. Sir, I have not discussed the President's budget with the advisory committee.

Mr. FOGARTY. What was your original suggestion for 1964?

Dr. CUMMINGS. The amount originally requested was \$4 million.

Our program director, Dr. Leavitt, has informed me that he will be able to maintain a vigorous program at the reduced level.

Mr. FOGARTY. Well, I have heard that answer 700 times over the years.

Dr. SHANNON. The fact of the matter is that it becomes possible to maintain this at the present level within the \$3 million figure, primarily because we are over the period of initial equipment costs, but realistically, this maintains the program at the present level.

NEED FOR MORE PROJECTS

Mr. FOGARTY. It seems to me with only five projects it is not much of an international program. I would just guess offhand you would get good results and it would be worthwhile to have two or three more in South America.

Dr. CUMMINGS. There has been an interest expressed.

Mr. FOGARTY. You have one in Colombia.

Dr. CUMMINGS. Yes; one in Colombia and one in Costa Rica. There has been an interest expressed by several American universities about the possibility of developing centers in South America. We would receive a proposal, a well-developed proposal, if one were forthcoming, with an open mind.

INTERNATIONAL ACTIVITIES OF NIH

Mr. FOGARTY. Tell us about your other international activities, your current program, plans for the future and why they are important. Take research first, training second, and fellowships third.

Dr. CUMMINGS. Yes, sir.

FOREIGN RESEARCH GRANTS

Well, first, I should call to the committee's attention or remind the committee that the direct support of research out of this country by NIH takes place through support by individual NIH institutes and divisions. We believe that such support is not only important, but necessary. Historically, certainly prior to World War I, the flow of medical knowledge and information was from Europe to the United States, as was brought out in yesterday's discussion. The United States reached a position of eminence during the period between the two wars, and as Dr. Shannon commented, since World War II we have preempted leadership in medical science. However, there must remain this renewed flow of skills and talents between countries. Thus I believe that on general grounds we are compelled to be involved in the international scientific community.

But specifically, and perhaps more importantly, the National Institutes of Health must be in a position to be able to capitalize upon the unusual skills, talents, or resources which exist in other countries. We have no monopoly on these things.

Now, in terms of logistics and actual accounting for our foreign research grants during the past fiscal year, we supported research through the institutes and divisions totaling \$13.5 million. This amount supported approximately 800 individual foreign research grants.

I should point out that these grants are made through the usual competitive mechanism, but in addition we have imposed new criteria which make it more difficult for a foreign scientist to actually have a grant awarded than a domestic scientist.

The new criteria relate to U.S. science policy generally, and perhaps in part to our own philosophy.

First, we no longer pay the indirect costs for the support of research abroad. This was done to some degree to allow the host institution abroad to participate with us; to collaborate at least to the extent that they contribute the indirect costs.

Second, only highly selected projects are supported. This is enforced by allowing only those grants which receive a priority better than the domestic mean to be paid. Third, Mr. Chairman, in order to avoid a possible dependence on the United States and specifically on NIH, we have usually limited our commitments abroad to a 3-year period.

Mr. FOGARTY. What about the funding?

Dr. CUMMINGS. The funding for research grants abroad takes place through the regular research grants budget of the various institutes. There is no budget available in the Office of International Research for these grants.

RESEARCH TRAINING GRANTS

Now, in answer to your question about support of research training, this is a very vital element of our international activities, because it provides a two-way scientific flow. NIH provides support of the training of Americans in foreign institutions through the provision of fellowships and traineeships.

On the other hand, we provide the support for training of foreign scholars and scientists in American institutions through the provision of international postdoctoral research fellowships. Last year we brought to the United States 92 foreign scientists for training in American institutions spending \$700,000. In addition, a small grant is provided for the returned fellow in order to begin or keep his research going when he returns to his home institution.

Mr. FOGARTY. How does that benefit this country?

BENEFITS FROM TRAINING FOREIGN SCHOLARS IN THIS COUNTRY

Dr. CUMMINGS. We believe this benefits this country in several ways. These men who come to this country begin work on a problem of interest to the United States and then return often to work on the same problem in their own environment. We also think it will have an important secondary effect insofar as a personal linkage develops between the scientist who returns and his preceptor in this country. We have seen some evidence of collaborative research develop as a result. So I firmly believe that these fellowships will redound to the health of the American people.

Dr. SHANNON. May I interrupt?

The thing is, Mr. Fogarty, everybody views these programs differently, and I would like to make a personal comment on this point as to the value of these programs to this country, which, although intangible, I think may well be its most important value.

In the first place, this is a highly selective program. Ninety-odd students from some 35 countries. These people are nominated by the country where they originate, in national competition. These are the brightest students from these countries who come from such intellectual centers as the country has and I think that the primary

benefit is the progressiveness of these people. Some of their time is spent—some of them spend their time at NIH. The bulk go into the university world and progressively rotate through, and our young graduate students who have continuing day-to-day exposure to these things begin to grab some concept of the foreign stream of thought, the things that make other national sciences comparable to their own. These people bring new ideas, new approaches into our own domestic laboratories and the intermixing that results, since these are extraordinarily superior people coming from very highly developed areas, has a profound effect on our own domestic training. This is intangible. This is not amenable as to the benefit, but I can't help feel that this is the most direct benefit we get.

Mr. FOGARTY. Go ahead.

Dr. CUMMINGS. I certainly share that view.

AMERICAN SCHOLARS SELECTED FOR FOREIGN TRAINING

Well, sir, we have training grants abroad. These are small in number, usually conceived with the hope and inspiration that the support of the center in a foreign institution will provide the American scholar an unusual opportunity to acquire new research methodology and technology.

Mr. FOGARTY. Will you put in the record how the American scholar is selected?

Dr. CUMMINGS. Yes, sir.

(The information follows:)

Americans being trained abroad as postdoctoral fellows or special fellows are selected, initially, by one of the Fellowship Review Panels (administered by the Career Development Review Branch, Division of Research Grants, NIH). An appropriate categorical review panel (from among the 12 presently organized) recommends those individual applicants believed to be suitable for training in institutions of the United States or abroad. These recommendations are received and acted upon by the individual categorical institutes of the NIH which conduct fellowship programs. Only under exceptional and rare circumstances are predoctoral fellowships awarded for training outside of this country; postdoctoral or special fellowships may support training abroad when satisfactory evidence is furnished that training suited to his purpose is best obtained abroad. Direct traineeships may support studies in oversea institutions when satisfactory justification is provided that the type or quality of training is particularly indicated in the applicant's case. These awards may be recommended by national advisory councils after initial review by an extramural training committee organized by the Institute which conducts the program. A few training grants have been made to outstanding scientists in foreign institutions who are prepared to provide research training not obtainable in the United States to young American scientists. In these cases, selection of trainees is made directly by the program director.

Dr. CUMMINGS. The American scholar who wishes to work abroad competes in a sense as we would for a domestic fellowship. He puts up his proposition which is reviewed at NIH, and if approved he is permitted travel funds and a stipend for study in approved foreign institutions. I think it fair to point out that the reverse flow in this type of operation is much larger. Many foreign physicians and scientists come into our domestic training grants, perhaps through internship and residency training in this country and then are invited to re-

ceive research training in a domestic research grant, or, in some cases, through direct application for an appointment in a domestic training grant.

We have been carefully studying this problem, Mr. Chairman, because there was some concern that the numbers may reach a point where the research opportunity for the foreign scholar might not match his training upon return to his home country. Dr. Kelly West, in my office, has recently completed a most interesting study of this situation which sometime I would like to have the opportunity to share with this committee.

At present, about 10 percent of trainees are foreign nationals. Now, out of context, this would appear to be an inordinate number, but in the general scheme of things, when you recall that 40 percent of American Nobel Prize winners are foreign-born and about 20 percent of American professors and scientists who are doing research in this country under our sponsorship are foreign born this is a reasonable proportion. In fact, I was surprised to learn that about 6 percent of the general population of this country is still foreign-born. So that although we have expressed some interest and concern in the aggregate numbers—1,250—we are more relaxed about the training program vis-a-vis the domestic requirement.

I hope that answers your question.

Mr. FOGARTY. It does, and you can elaborate on this in the statement for the record.

(The statement referred to follows:)

INTERNATIONAL ACTIVITIES OF THE NATIONAL INSTITUTES OF HEALTH

I. BACKGROUND AND LEGISLATIVE AUTHORITY

Growth of medical knowledge in the United States up to World War I depended to a large extent on the flow of information and knowledge from Europe. Our own medical research, which became of age between the two World Wars, was then subjected to even greater demands by the increasing recognition of the importance of medical research associated with the rising standards of living and medical care which followed World War II.

The renewed flow of skills and ideas from Europe facilitated the spectacular growth in scope and productivity of American medical research following World War II. It was during this period when the United States was coming into a position of world leadership in medical research that the basic interdependence between Europe and America for stimulation of ideas and interchange of skills came to be understood as necessary for rapid progress of medical science both nationally and internationally.

Early official U.S. recognition of the usefulness of foreign research resources and talents in throwing light on our domestic medical problems was in the 1930 act of Congress which (in establishing the National Institutes of Health) authorized fellowship arrangements for sending American scientists overseas for training and to carry on investigations in foreign localities or in collaboration with foreign scientists. The concept was greatly broadened in Section 301 of the Public Health Act of 1944 and related legislation establishing the

categorical research institutes which authorized the present grant and fellowship programs and permitted them to be conducted both in the United States and abroad.

Explicit legislative recognition of the importance of international medical research activities to progress of the health sciences in the United States came in the International Health Research Act of 1960 (Public Law 86-610). This act authorized the Surgeon General of the Public Health Service to carry on "cooperative endeavors with other countries in health research and research training." In the same act Congress recognized a permanent U.S. interest in international cooperation to further the "international status of the health sciences," an interest which had previously been manifested mainly through the various foreign aid programs. The act authorized the President to carry out "cooperative enterprises in health research, research planning, and research training."

This authority has been exercised by the National Institutes of Health under limited and specific delegations in such instances as the financial assistance provided to the World Health Organization and the Pan American Health Organization through research planning grants.

II. PHILOSOPHY

The National Institutes of Health have in recent years greatly increased the use of foreign scientific resources to carry forward their medical research objectives. By selecting appropriate projects among the many opportunities offered abroad, the Institutes are supplementing domestic resources both in quantity and scope. Thus, our own supply of highly trained scientists in certain fields is being reinforced by grants affording partial support for outstanding foreign scientists working on projects of mutual interest and concern.

Use of foreign scientific resources and environments not only adds unusual talent and the stimulation of other ideas, but it affords a greater variety of techniques and approaches to solve problems related to causation, prevention, and treatment of diseases of importance to the American people as well as those of other nations. For example, geographic pathology and epidemiology studies carried on among contrasting national and ethnic groups make it possible to identify groups with differing susceptibility to certain diseases. Intensive studies of genetic and environmental factors related to such groups may furnish important clues to the causes of disease not readily evident from studies restricted to our own environment.

The international activities of the National Institutes of Health is not a separate program with its own objectives. Rather it represents the aggregate of the foreign segments of the programs of the categorical Institutes which are directed toward advancing the health sciences in the United States, and thereby the health of the American people.

Collaboration of foreign scientists and institutions is, for the most part, readily offered because few of the health problems of the American people are unique. Most of them represent equally serious problems for other countries. This mutuality of interest leads to a ready interrelationship and interdependence which is the basis for scientific cooperative efforts.

III. SCOPE OF INTERNATIONAL SCIENTIFIC ACTIVITIES

The NIH international scientific activities have grown both in scope and magnitude in recent years. Generally, these activities fall within one or more of three general types: Support of research projects, support of research training, and support of research communications, i.e., interchange of information and skills. The principal international activities and the funds expended for their support are listed in table I. The geographic distribution of the major programs is shown in table II.

U.S. PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

TABLE I.—*Principal international activities, by program, fiscal year 1962*

Activity	Number of awards	Amount
Total.....		\$29,675,603
Support of medical research, total.....		17,449,118
Research project grants:		
To investigators in foreign countries.....	774 grants.....	11,793,859
To international organizations.....	30 grants.....	1,411,559
Research contracts with foreign organizations.....	5 contracts.....	173,616
Collaborative agreements financed under Public Law 480.....	29 projects.....	3,017,624
Foreign scientists and research associates under visiting program.	190 scientists.....	1,052,460
Support of research training, total.....		11,872,242
Americans studying abroad under fellowship program.....	243 fellowships.....	1,804,786
Americans studying abroad under traineeships.....	36 traineeships.....	402,062
Foreign institutions receiving training grants.....	13 grants.....	380,299
Foreign research fellows studying in the United States.....	92 fellowships.....	692,095
Estimated foreign research trainees under training grants to U.S. research institutions.	1,250 trainees.....	6,500,000
International centers for medical research and training.....	5 grants.....	2,093,000
Support for medical research communications, total.....		354,243
Grants to international professional organizations located abroad for support of international meetings.	4 grants.....	116,992
Grants to support translation abroad and publication of foreign medical literature.	8 grants.....	237,251

Note on coverage.—Does not include direct operation of research laboratories in Ghana, the Canal Zone, Malaya, and east Pakistan; projects conducted in co-operation with other Federal agencies through the Interdepartmental Committee on Nutrition in the National Defense; field trials and investigations overseas conducted as an incidental part of intramural and domestic grant projects (e.g., the pilot study in Upper Volta of immunization by attenuated measles vaccine involving two trips by a NIH team of virologists). The figures on grants supporting international meetings cover only grants to professional organizations located abroad; the total of such grants to domestic and foreign organizations was 46 and the amount \$840,262.

TABLE II.—Selected major international activities by program and country, fiscal year 1962

Country	Research grants		Research con- tracts		Visiting scientists		U.S. fellows abroad		Traineeships abroad		Training grants		International research fellows	
	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount
Total.....	816	\$13,559,661	5	\$173,616	190	\$1,052,460	243	\$1,804,786	36	\$402,062	13	\$380,299	92	\$692,095
Western Hemisphere, total.....	196	3,312,944	2	128,866	18	86,957	17	103,112	1	8,800	8	240,969	26	188,165
Canada.....	108	1,893,997	—	—	7	30,469	12	71,255	1	8,800	6	147,019	—	—
Latin America, total.....	88	1,448,947	2	128,866	11	56,498	5	31,857	—	—	2	93,950	26	188,165
Argentina.....	16	202,368	—	—	1	7,000	—	—	—	—	—	—	1	9,120
Brazil.....	13	123,478	—	—	4	15,088	—	—	—	—	1	32,400	4	28,347
Chile.....	10	105,195	—	—	1	7,820	—	—	—	—	—	—	3	18,305
Colombia.....	4	32,763	—	—	1	11,155	—	—	—	—	—	—	4	30,659
Costa Rica.....	1	7,475	1	21,000	—	—	—	—	—	—	—	—	2	13,910
El Salvador.....	1	14,795	—	—	—	—	—	—	—	—	—	—	—	—
Guatemala.....	1	7,500	—	—	—	—	—	—	—	—	—	—	—	—
Jamaica.....	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Mexico.....	15	205,808	1	107,866	1	4,165	4	26,227	—	—	1	61,550	1	6,264
Panama.....	6	175,512	—	—	—	—	—	—	—	—	—	—	2	16,643
Peru.....	12	359,672	—	—	—	—	—	—	—	—	—	—	—	—
Uruguay.....	6	107,441	—	—	3	11,260	—	—	—	—	—	—	4	30,328
Venezuela.....	3	106,940	—	—	—	—	1	5,630	—	—	—	—	3	20,659
Europe, total.....	354	5,357,206	2	32,250	79	410,101	207	1,542,672	33	371,402	3	91,400	43	298,038
Austria.....	8	50,088	—	—	3	21,823	—	—	—	—	—	—	4	24,993
Belgium.....	16	212,609	—	—	—	—	3	18,621	—	—	—	—	1	240
Denmark.....	21	190,026	1	14,750	2	3,680	14	95,132	3	31,500	—	—	2	16,141
Finland.....	18	175,410	—	—	3	6,417	—	—	—	—	—	—	4	30,686
France.....	44	872,547	—	—	2	6,187	22	173,850	2	20,625	—	—	1	30,417
Germany, Federal Republic of.....	11	82,720	—	—	12	68,576	17	142,335	3	32,990	—	—	3	23,109
Greece.....	2	14,775	—	—	1	7,500	—	—	—	—	—	—	1	7,342
Iceland.....	2	35,528	—	—	—	—	—	—	—	—	—	—	—	—
Ireland.....	7	64,001	—	—	1	1,749	—	—	—	—	—	—	3	20,484
Italy.....	30	327,709	1	17,500	12	66,669	9	59,934	—	—	—	—	4	28,523
Netherlands.....	13	148,324	—	—	2	21,181	4	27,922	—	—	1	41,000	1	8,640
Norway.....	9	98,326	—	—	1	5,670	3	17,648	—	—	—	—	1	7,216
Poland.....	—	—	—	—	1	1,772	—	—	—	—	—	—	3	24,757
Portugal.....	1	8,855	—	—	—	—	—	—	—	—	—	—	—	—
Spain.....	2	13,080	—	—	—	—	—	—	—	—	—	—	3	16,373
Sweden.....	67	1,336,505	—	—	2	7,603	—	—	—	—	—	—	4	32,421
Switzerland.....	14	172,963	—	—	5	30,405	31	234,095	7	74,074	2	50,400	—	—
United Kingdom.....	87	1,521,140	—	—	8	46,405	14	108,454	—	—	—	—	4	11,040
Yugoslavia.....	2	32,000	—	—	22	113,796	90	664,681	17	203,203	—	—	4	25,349
	—	—	—	—	2	6,668	—	—	—	—	—	—	5	30,327

See footnotes at end of table.

TABLE II.—Selected major international activities by program and country, fiscal year 1962—Continued

Country	Research grants		Research con- tracts		Visiting scientists		U.S. fellows abroad		Traineeships abroad		Training grants		International research fellows	
	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount
Africa, total.....	21	\$465,322			3	\$22,145							1	\$8,463
Congo, Republic of.....	1	10,235												
Kenya.....	1	17,180												
Liberia.....	3	110,171												
Nigeria.....	2	92,300												
South Africa, Republic of.....	12	193,811			3	22,145							1	8,463
Tanganyika.....	2	41,625												
Middle East, total.....	78	1,176,342			16	86,236	7	\$64,326	1	\$8,860			5	45,429
Iran.....						4,500								
Israel.....	60	951,466			1	38,956	6	56,922					2	19,300
Jordan.....	1	54,489			9								3	26,129
Lebanon.....	16	161,187			2	22,970	1	7,404	1	8,860				
Turkey.....	1	9,200			2	12,812								
United Arab Republic.....					2	6,998								
South Asia and Far East, total.....	125	1,482,045	1	\$12,500	71	410,046	12	94,676	1	13,000	2	\$47,930	17	151,980
Australia.....	26	483,564			5	23,304	5	40,866	1	13,000			3	27,755
Hong Kong.....	1	9,214												
India.....	6	54,646			18	114,953	1	5,975					2	16,410
Indonesia.....					1	12,470								
Japan.....	82	868,543	1	12,500	40	215,822	5	40,965			2	47,930	3	24,852
Korea.....	2	15,012			1	7,497								
Malaya.....	1	10,791											3	26,966
New Zealand.....	1	12,090				9,000	1	6,870					1	8,770
Pakistan.....	2	12,990			3	17,626							1	9,708
Philippines.....	2				1	1,374							3	29,639
Taiwan.....	3	15,195			1	8,000							1	7,880
Thailand.....														
Stateless, total ²					3	36,975								

IV. SUPPORT OF MEDICAL RESEARCH

As indicated in table I, the principal mechanisms involved in NIH support of research overseas are research project grants to foreign investigators and international organizations, research contracts, and collaborative research project agreements financed by foreign currencies derived from sales of agricultural surpluses (Public Law 480).

Research grants.—The total number of research grants to foreign investigators and international organizations increased from 573 in fiscal year 1961 to 816 in 1962, and the amount awarded from \$9,210,946 to \$13,559,661. Foreign grants also increased in importance within the research grants program: from 3.4 percent in fiscal year 1961 to 4.3 percent of the total of regular research grants in fiscal year 1962. In this calculation, grants for general research support made for the purpose of enlarging and improving the research resource base are not included, because grants for this purpose are not made to foreign institutions.

The rapid growth of foreign applications for research support gave rise during fiscal year 1962 to the following measures designed to insure greater selectivity and scientific excellence in award of grants to foreign investigators and to control their growth.

(a) More restrictive criteria were applied in selection of foreign projects. Foreign awards were limited to projects which were scored better than the average for all applications recommended for approval by the scientific reviewing bodies. To be eligible for support, foreign proposals have had to meet the following criteria:

(1) The research proposed (a) is outstanding or original in concept, or (b) would utilize skills, materials, or other resources not likely to be available in the United States; and

(2) The proposal is of such a nature that the results are likely to advance significantly the status of the health sciences in both the country of the applicant and the United States.

(b) The burden of indirect costs was shifted to recipient institutions.

(c) Duration and magnitude of commitments to foreign institutions were restricted by limiting commitments to 3 years and a maximum of \$100,000 in any year except in unusual circumstances. These restrictions are complementary to the existing policy which limits general program support and resource development types of support to domestic institutions.

(d) A dollar ceiling was imposed to limit total foreign research grants to 4 percent of funds available for regular research grants (excluding the resource development type of grant).

(e) NIH scientific offices were established in Europe and Latin America and arrangements were underway for similar representation in the Far East and south Asia, to increase NIH capacity to evaluate research proposals, and to study the effect of NIH activities on medical science in these areas.

The immediate result of these measures has been to limit foreign grants in fiscal year 1962 to \$13.5 million, where under previous approval rates the total might easily have reached \$18 million. Also, the rate of awards against new applications was reduced from about 50 percent to 33 percent.

Analysis of the effect of these measures as well as the influence of NIH grants on local support of medical research overseas which began in fiscal year 1962 will accelerate with the availability of new overseas scientific representation. Information from these representatives will assist study sections, councils and Institute staffs in the appraisal of foreign proposals and help answer such questions as: will a grant inhibit or stimulate local support of this and related research?

Efforts are continuing to assure increasing local financial participation in medical research projects supported by the NIH, particularly in countries of clear economic capability. However, because these countries are the ones which are most productive in fields of medical research and of greatest interest and concern to the United States, it will always be necessary to maintain a close interrelated common research effort. Nevertheless, the possibility is being explored of eliminating salaries of principal investigators from NIH support of research projects overseas. Aside from the immediate savings and greater feasibility of withdrawal of NIH funds after they had performed a priming function, this would have the advantage of assuring that firm control of the development of science in the country concerned rested not with the NIH but with the country's own scientific leadership.

Collaborative research agreements under Public Law 480.—Foreign currencies generated from the sale of surplus American agricultural products are available for medical research purposes in a limited number of countries. The NIH uses these funds to support collaborative agreements with research institutions in such countries for research on disease problems important both to the country concerned and the research effort of the Public Health Service. During fiscal year 1962, \$3,017,624 were obligated for 29 projects in 6 countries: Brazil, Egypt, India, Israel, Pakistan, and Poland.

Visiting scientist program.—Productive scientific relations and collaboration between the NIH laboratories and foreign research centers are greatly facilitated by the visiting scientist program authorized in 1950 by section 207 (f) and (g) of the Public Health Service Act.

This enables NIH to employ a limited number of distinguished citizens or noncitizens where civil service or Commissioned Corps appointments are not feasible, and to facilitate rapid exchange of scientific and technical information. In fiscal year 1962, 190 foreign scientists were employed at a cost of \$1,052,000 for salary and travel expenses.

V. SUPPORT OF RESEARCH TRAINING

Foreign-trained scientists and foreign nationals trained in the United States are contributing very significantly to the manpower base for medical research in the United States. This input now accounts for about 20 percent of the Ph. D.'s and M.D.'s entering research. Continuation of this input will assist materially in achieving the goal of doubling of American medical research manpower by 1970.¹ Overall, in fiscal year 1962, NIH obligated \$143,800,000 for training and fellowships related to this goal. About \$11,900,000 was for the training of foreign nationals in the United States and training of American scientists abroad. Description of the major international elements in the training program follows.

Fellowships and traineeships.—The international segment of the overall fellowship program operates through:

(a) Awards for study and research at foreign institutions made to U.S. nationals under the same general conditions as for postdoctoral fellowships at domestic institutions. There were 243 such fellowships awarded in fiscal year 1962 with stipends and travel amounting to \$1,804,786 including \$63,306 in related supply grants (limited to \$500 per fellow) for small equipment and materials to facilitate his research.

(b) The international postdoctoral fellowship program for study by foreign scientists in the United States which is administered under special conditions. This program is described fully below.

(c) Traineeships in specialized medical research areas and techniques awarded to postdoctoral research investigators for study in foreign institutions. In fiscal year 1962, 36 awards were made for foreign training at a cost of \$402,000.

International postdoctoral fellowship program.—As part of the regular Public Health Service fellowship program dating from the 1930's, awards to promising foreign scientists to prepare for careers in biomedical research have become a significant factor since 1958. Although these fellowships undoubtedly help build research capabilities in other countries, the program retains a basically domestic orientation. One purpose is to enrich postgraduate biomedical training in this country by enabling foreign investigators to share their ideas and background with American colleagues. Another is to encourage foreign scientists to participate in research bearing upon American health problems—research which is often continued and extended by the fellow upon return to his home country, thus generally enhancing opportunities for future collaborative efforts.

The fiscal year 1962 appropriation of \$700,000 supported 92 fellows. To provide some of the resources needed in starting a medical research career and make optimal use of their U.S. training, research grants up to \$2,500 per year for 3 years are available to international fellows newly returned to their home countries. During fiscal year 1962, \$83,287 was awarded for an initial year's support of 16 research projects of such fellows and for continued support of 16 ongoing projects.

New national fellowship nominating committees were set up during fiscal year 1962 in Venezuela and Costa Rica, bringing the total to 41 participating countries

¹ Report on Manpower for Medical Research, pt. 4, hearings before a subcommittee on Department of Health, Education, and Welfare Appropriations for 1962 of the House Committee on Appropriations, 87th Cong., 2d sess.

authorized to submit four candidates for selection by the NIH awards panel. In fiscal year 1963, nominating committees will be formed in three or four additional countries, and all of the participating countries will be encouraged to name up to six candidates. A followup survey of foreign fellows who completed their studies 2 or more years ago is being undertaken to determine the effectiveness of this program. The study will cover such factors as relation of present work to training, his present institutional setting, and allocation of his time to research teaching, administration, and clinical practice.

Training grants.—The NIH training support is accomplished through grants to U.S. academic institutions in behalf of highly qualified scientists who supervise and conduct the training. These grants provide stipends for trainees and certain research costs related to the training. In this way NIH supports about 12,000 research trainees each year.

Under special conditions young foreign scientists may participate in this training at U.S. institutions. In fiscal year 1962 about 1,250 or 10 percent of these research trainees were foreign nationals. Support of these part-time or full-time stipends for foreign trainees resulted in an expenditure in fiscal year 1962 of \$4.3 million. Since research training costs other than stipends were involved it is estimated that the total expense of foreign participation totalled \$6.5 million in fiscal year 1962, about 4.5 percent of the NIH investment for research training. Participation of these young investigators from abroad furthers U.S. research objectives in several ways. They provide an immediate and productive source of manpower, since they carry out important research in the course of their training. They often bring to our research programs new skills, fresh ideas, and sometimes special techniques. Upon their return to their home countries, they may use their U.S. training in research of importance to American health problems even though their subsequent work is carried out in a foreign country and supported by that country. Lastly, many continue to collaborate with and assist their American preceptors in the research begun in the United States. Despite these benefits, the NIH intends to study the mechanisms, terms, and conditions of these appointments with a view to directing them more selectively and specifically toward needed areas of research manpower development.

A few training grants have been made to outstanding scientists in foreign countries who are prepared to transfer some of their skill and special approach to young scientists. In fiscal year 1962, 13 such grants involving \$380,000 were made in 6 countries: Brazil, Canada, Mexico, Netherlands, Sweden, and Japan. Up to fiscal year 1962, a portion of these grant funds could be used for stipends to nationals of the country where the training project was located. Under all new grants to foreign institutions, stipends are available only to U.S. citizens in training there.

International centers for medical research and training.—Five centers now have been established through collaborative agreements between American medical schools and a foreign medical research institute: the University of California with the Institute of Medical Research, Kuala Lumpur, Malaya; Tulane University with University del Valle, Cali, Colombia; Johns Hopkins University with Calcutta School of Tropical Medicine, India; Louisiana State University with University of Costa Rica, San Jose; and University of Maryland with Institute of Hygiene, Lahore, West Pakistan.

Each of the international centers consists of two operational elements: (1) a research and research training activity in the United States including both American and foreign medical investigators which is closely related to (2) specific research and training conducted in the oversea institution where American scientists may have the advantage of conducting research under unusual environmental, ethnic, and medical conditions not available for study at home. While oriented generally toward the need of American physicians and scientists to have the stimulus of research in foreign settings, a corollary advantage of the centers is the stimulus and experience afforded the foreign collaborating institutions to develop and expand indigenous medical research and training resources. The centers were supported in fiscal year 1962 by grants totalling \$2,093,000 to the five American universities concerned. These grants cover costs for a 1-year period, against an overall commitment for 5 years' support.

The initial phase of program development has been completed for each of the centers, and research is now underway at each foreign site. This involved the administratively complex job of concluding agreements satisfactory not only to the two private institutions involved in each case, but also meeting the requirements of the United States and the foreign government concerned. Staffing also

was involved, and each of the centers has been successful in attracting well-trained young scientists interested in experience and careers in international research. Each of the centers will be moderately expanded in the second phase through staff additions so that a multidisciplinary team approach can be brought to bear on the complex biomedical problems at the foreign research sites.

International research associates program.—This new program, which goes into operation in fiscal year 1963, was developed to assure that there will be available to the Public Health Service an adequate number of highly capable internationally oriented U.S. investigators. Eight to ten Public Health Service Commissioned Officers will be assigned each year to research projects carried out overseas by PHS units or to projects of special interest to the Service carried out by other organizations. Thus research experience and training of high quality and interest can be assured, and at the same time fulfill an important need of the PHS by supplying additional skilled manpower in support of foreign projects. The budget for fiscal year 1963 amounts to \$150,000.

VI. INTERNATIONAL MEDICAL SCIENCE COMMUNICATIONS

Major support is being given by the NIH to three of the four basic elements or functional processes² involved in biomedical communications: the personal interchange among scientists, publication of findings, and the training and educational process.

Formal meetings, seminars, symposia and other activities arranged by scientific, professional and related organizations, which form the basic framework of the process of personal interchange among scientists, have come to have major importance in scientific communications. As an integral part of many NIH programs and activities, support is provided for this important personal interchange process as a basic means of enlarging communications in biomedical sciences.

In fiscal year 1962, NIH awarded 46 grants totaling \$480,000 for partial support of international scientific meetings in the United States and abroad and for travel by selected American scientists to participate in such meetings. These grants are made to scientific and professional organizations which also select appropriate U.S. participants to receive travel assistance. Additional support for medical communications is provided by allowing investigators having NIH grants upon specific approval to use grant funds for travel to international scientific meetings related to the grant project. This represents a change from the previous policy of relying on the institution to approve the use of grant funds to cover the investigator's travel to international meetings in accordance with its internal policy.

It has been estimated that 60 percent of world biomedical research literature is in languages infrequently read by American scientists. Thus an important international objective of the Public Health Service (the National Institutes of Health and the National Library of Medicine, specifically) is to find means of encouraging the translation and publication of foreign literature of importance to American medical science. NIH support of primary publications, bibliography, and abstracts (e.g., Cancer Chemotherapy Reports, Psychopharmacology Abstracts, World Neurology) makes a major contribution to international science communications. Specific support of foreign institutions for translation, abstracting, and publication of the less accessible medical literature in fiscal year 1962 included eight grants to Excerpta Medica Foundation in Amsterdam, amounting to \$237,000.

VII. ADMINISTRATION

Responsibility for policy formation, program analysis and coordination of foreign and international activities of the National Institutes of Health is in the Office of International Research, a staff arm of the Office of the Director, National Institutes of Health. Creation of this office was motivated by the need for special attention to these activities which have expanded rapidly in magnitude and complexity in recent years, and to give specific expression to the purposes stressed in the International Health Act of 1960. The Office of International Research directly administers the NIH part of the Special Foreign Currency program financed from Public Law 480-derived funds, the International

² These processes are outlined and discussed in "Communication in the Biomedical Sciences"—a report by the National Institutes of Health, Mar. 9, 1962. Reprinted in hearings before Subcommittee on Department of Health, Education, and Welfare Appropriations for 1963, House Committee on Appropriations, pt. 3, p. 1595.

Centers for Medical Research and Training, the International Postdoctoral Fellowship programs, and the new International Research Associate program, all of which have been discussed above.

To fulfill its responsibilities for evaluating medical research and scientific manpower opportunities not available in the United States and to stimulate the flow of information on medical research underway in other countries, NIH now has established overseas offices and scientific representatives in Paris for Western Europe, London for the British Isles, Rio de Janeiro for Latin America, Tokyo for the Pacific area, and New Delhi for south Asia.

LEVELING OFF OF RESEARCH GRANTS PROGRAM

Mr. FOGARTY. Doctor, most of the increase you are requesting is for research grants—an increase of \$9,559,000; but all of this increase is for continuing grants and increase in overhead payments. Have you decided to level this program off?

Dr. POWELL. Sir, we think it is entirely possible to do some adjusting within the new grants as against the continuations and supplemental needs so that it will be possible to award new grants in fiscal 1964.

Mr. FOGARTY. Under this \$9,559,000, you are not going to make much progress. The justifications show you are going to fund the same number of new applications as you did in 1963.

Dr. POWELL. This does not mean no increase in new applications and new grants. It means no increase—

Mr. FOGARTY. The way I look at that, you are not going to show much progress in 1964 over 1963. It looks to me like you are leveling your program off with this sort of budget.

Dr. SHANNON. Mr. Fogarty, I think that Dr. Powell did not make clear that taking the 1963 base over and above supporting—he will be able to finance the same number of wholly new applications next year as he was able to finance this year from the 1962 base.

Mr. FOGARTY. That is what I said. That was my statement. And my conclusion was that it does not allow for much progress for 1964 over 1963.

Dr. POWELL. Sir, it is not a matter of leveling off the program. It is a matter of leveling off the rate of growth of the program.

Mr. FOGARTY. What is the difference?

Dr. POWELL. The program itself will increase by the same amount that the program increased last year in terms of new grants.

Mr. FOGARTY. What did you have for new grants in 1962? The dollar figure is the same in 1963 as 1964—\$15,549,000 in 1964 and in 1963. What did you have in 1962?

Dr. POWELL. \$16,890,000.

Mr. FOGARTY. So you are going downhill then, according to that.

Dr. POWELL. Not from 1963 to 1964.

Mr. KELLY. I think 1962 includes activities that we transferred out of NIH in 1964.

Dr. POWELL. Yes, sir. And as a matter of fact, the 1963 figure, in our best estimate at the moment, will provide sufficient funds to pay all of the new grants as well as the continuations and supplementals which are approved during fiscal 1963.

Mr. FOGARTY. Well, I still don't see how it can be argued that this is not leveling off the program when you budget for exactly the same number of new projects next year as you plan to fund this year.

AREAS OF SPECIAL EMPHASIS IN TRAINING GRANTS

The next largest increase is \$3,580,000 for training grants. Are you going to apply this across the board or are there particular fields of training that will get special emphasis?

Dr. POWELL. Well, we will be giving special emphasis to certain areas of training.

Mr. FOGARTY. What are they?

Dr. POWELL. These are the biophysical sciences, biomedical engineering and perhaps most especially, behavioral sciences.

Dr. SHANNON. May I interject a comment there?

We discussed with Dr. Powell, and you might wish to bring out in further testimony, one of the administrative problems he faces in these programs is to separate out a substantial amount of both research grants and training grants as part of the base of the new Child Health and Human Development Institute. A substantial amount of training funds at this new institute will be derived from Dr. Powell's current appropriation.

INCREASE IN FELLOWSHIP ALLOWANCES

Mr. FOGARTY. You mention on page 28 that you have increased the fellowship allowance to \$2,500 per fellow. How does that compare with other agencies? What was it last year?

Dr. SHANNON. This is comparable with the National Science Foundation and pretty much the same in the case of all other agencies other than the Space Agency. Unfortunately, the Space Agency has elected to establish a program at a considerably higher level and we feel that this is going to cause complications.

Mr. FOGARTY. How much is the Space Agency?

Dr. SHANNON. I don't have the precise figure. It is close to a thousand dollars more.

Mr. FOGARTY. What was it last year?

Dr. POWELL. It was not a fixed amount last year for NIH predoctoral fellowships, and this \$2,500 allowance is for predoctoral fellowships only. It averaged about \$1,300 last year. It was calculated on a different base, namely, tuition, supply grants, and travel.

Mr. FOGARTY. On what is this based, this \$2,500 as compared to last year?

Dr. POWELL. The \$2,500 per fellow is now a flat allowance that goes to the institution, rather than an individual calculation based on the considerations I mentioned.

Mr. FOGARTY. Does that mean that the institutions are making money on this?

Dr. POWELL. No, sir.

Dr. SHANNON. As a matter of fact, this was taken up in conjunction with the National Science Foundation and became abundantly clear that in the absence of more adequate servicing of the schools' needs, the predoctoral fellows were not getting the training experience that we feel is essential and we jointly agreed that at the very minimum, the \$1,300 on the average should be increased to \$2,500. This against a background of studies that were conducted in part for the President's Science Advisory Committee in relation to the manpower panel that

had training of scientists under consideration for the past 12 or 18 months is that their calculations, as with the training of physicians, the cost to the school, the training of a scientist is close to \$3,000 a year and in some specialties considerably above, but in very few much below. So that \$2,500 as a flat rate was selected because it is sufficiently low at the average that it would not require a detailed cost accounting to make this a valid payment. So that the \$2,500 is still estimated to be considerably below the average cost to the school.

Mr. FOGARTY. Is the same change being made in the other institutes?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. How much in total does this increase in allowances cost?

Dr. SHANNON. I would have to furnish that figure for the record, Mr. Fogarty.

(The information follows:)

The cost of this increase in the predoctoral allowance will be approximately \$2 million in 1963 and \$2.6 million in 1964.

Mr. FOGARTY. This is the first we have heard about this increase, is it not? We did not hear about it last year.

Dr. SHANNON. No, sir.

INCREASES REQUESTED FOR OTHER THAN PERSONAL SERVICES

Mr. FOGARTY. They are relatively small items but I notice that the amount you have budgeted for "travel and transportation of persons" is budgeted for 1964 at more than double the 1963 amount and the same is true of "rent, communications, and utilities." Why is that?

Dr. SHANNON. I could answer that problem in part. Maybe Dr. Powell might wish to go into detail. But contained within the funding of this appropriation are the basic administrative costs of three totally new activities; namely, the National Institute of General Medical Sciences, National Institute of Child Health and Human Development and the Division of Research Facilities and Resources under Dr. Stone. These three organizations were quite separate and will require substantially more in the way of administrative costs for such things as program analysis, program management, and program development. It is attributable to this factor that these funds were increased. These will be sorted out at a later time.

Mr. SEGGER. Mr. Chairman, one point here is that part of this is carried in 1963 in another part of the budget—i.e. the management fund. The operating costs of the Office of International Research for 1963 are reflected in the management fund and are not reflected in the 1963 base that you are looking at. So that the actual increase is much less than is shown in this table.

ANESTHESIOLOGY TRAINING PROGRAMS

Mr. FOGARTY. What are you doing in the field of anesthesiology?

Dr. POWELL. In anesthesiology, last year there were substantial funds made available specifically for training programs for research and academic careers in anesthesiology. Unfortunately, the number of suitable training situations which were deemed, by our consultants, worthy of NIH support is extremely limited. Therefore these funds

were not completely used. A report on this has been made available to the committee. We are still attempting to locate and assist in the development of suitable training activities, but as you have indicated, the supply of anesthesiologists is quite limited. Therefore, the supply of individuals and situations which permit meaningful training programs is also limited. We are conducting what staff work we can with cooperation of outside individuals and groups in attempts to increase the number of these training programs and get them moving.

Mr. FOGARTY. They do not have a closed or union shop, and not want any new trainees?

Dr. POWELL. Certainly not the people we have been dealing with.

Dr. SHANNON. Mr. Fogarty, this is a situation that has its counterpart somewhat in pathology. The market for well-trained pathologists in the small hospitals is so great and the salaries so attractive, and the conditions of work so pleasing, that the tendency for people trained to drain off into the service area is very good. Now, on the other hand, the training of an academic anesthesiologist is very complex because with the drugs available to him, with the chemical tools that are available to him and with his responsibility now, which goes far beyond the operating room, he really has to be very broadly trained, and especially in clinical pharmacology, above and beyond his ability to produce anesthesia in surgical patients. So that this training requires a fairly extensive exposure not only in the practice of anesthesiology, but also a very broad pharmacological training. On the other hand, for the practicing anesthetist, I would say the ordinary residency in anesthesiology departments of some 3 years is adequate for that person to go out and be very gainfully employed at a very substantial salary in a very enjoyable medical specialty. So the competition in this area is very brisk. The job we have set ourselves to, to train an adequate number of individuals such as are characteristic of those developed by Dr. Dripps and by Dr. Papper and the like, I guess will take 2, 3, or 4 years before we have an adequate number of training situations to produce the kind of people we are trying to produce.

Mr. FOGARTY. We will put in the record your special report on anesthesiology.

(The report referred to follows:)

SPECIAL REPORT: ANESTHESIOLOGY

BACKGROUND

Few people go through life without using some painkilling drug or anesthetic. However, very little is known about the way such agents work. There are a host of questions that research may hope to answer to insure improved safety in the use of these agents.

These deficiencies in our knowledge of anesthesiology have been clearly recognized by the scientific community for some time. The Senate Committee on Appropriations has anticipated the increasing public awareness of the problem by directing in 1961 that the Division of General Medical Sciences "give special attention to the training of research anesthesiologists and to the support of scientific research projects and program grants in anesthesiology." Last year the committee again recommended that the Division increase its efforts "in the field of anesthesiology for training grants in research anesthesiology and for special and career development fellowships."

STATUS OF RESEARCH

Answers to questions about the physiological reactions to anesthesia are being sought. Fundamental research into the molecular reactions by which so-called inert gases can produce the profound physiological changes associated with unconsciousness is now underway, but it will be some time before the significance of such studies is established.

One interesting project reported at the First International Congress of Oral Surgery in London and now in press in the *Journal of Oral Surgery, Anesthesia, and Hospital Dental Service*, is a review of a 4-year study at the National Institutes of Health entitled "General Anesthesia on Ambulatory Dental Patients." This project evaluated the effects of the common drugs and combinations of drugs used in dental surgery. Unlike most surgical cases, these patients walk into and expect shortly to walk away from their operations. The investigators of the National Institute of Dental Research found that pulse rate and blood pressure usually increase during these operations. They attribute the faster pulse rate to drug action and the rise in blood pressure to the stimulating effects of the surgery.

One current research effort to learn more about the causes of death from anesthesia is an analysis of the amount and distribution of anesthetics in tissues. Another study is being made of systems of continuous monitoring of the physiological changes in patients under anesthesia.

The largest multidisciplinary grants devoted to the study of the physiological effects of pain-relieving drugs on humans, where this is possible, and on animals where it is not, are not expected to reach completion and evaluation for some years.

There is need to know much more about the physiological reactions of different age groups with different disease conditions to specific anesthetics. The widening of the margin of safety and the reduction of deaths from anesthetics will depend upon future research on equipment, methods, and physiology. The reduction of anxiety and fear, and the psychological and behavioral aspects related to anesthesia need to be studied. And last, we still do not know the basis of consciousness and unconsciousness.

The reason there are so many questions and so few answers in the field of anesthesiology is due primarily to the fact that few clinicians and others interested in these questions have the training needed to search for answers.

STATUS OF RESEARCH TRAINING

In fiscal year 1963 the National Institute of General Medical Sciences has allocated \$328,114 to provide training for anesthesiology research at 11 institutions and 3 more grants are under consideration in the amount of \$113,178. From January 1962 to January 1963, 40 individuals took advantage of this program, a 37-percent increase in the number supported in the previous year. Also there are presently two postdoctoral fellows in the anesthesiology training program and one research career awardee supported in the amount of \$24,626. One other research career award was offered but declined by the applicant for financial considerations. Efforts are continuing to extend the interest of training institutions in this research area and to make sure that maximum use is made of available grant funds.

Although this report represents considerable expansion in the training support of anesthesiology over what it was merely 2 years ago, it is still quite inadequate in relation to the magnitude of the problem. Much more needs to be done to develop manpower in this critically shorthanded area. Most medical schools do not have a department of anesthesiology. Few of those that do are staffed to provide first-class environments for training in anesthesiology. It requires, in addition to the regular 4 years in medical school, several more years of inter-disciplinary training and a special motivation to produce a person capable of doing original research into the causes and effects of anesthesia, or, more important at this time, one able to train others to do fruitful research. It will take some years before this training effort can develop a base which will provide annually the research anesthesiologists the country needs. The young people we have just begun to interest in anesthesiology will need time to mature and to reach sufficient stature to staff new departments in medical schools and to arouse more interest in their field among university faculties and the medical profession in general.

When the primary objective is highly trained personnel, a crash program cannot substitute for the orderly process of growth. We anticipate that after a slow start, the increase in the number of carefully trained investigators will greatly extend the scope and value of anesthesiological research. During the next 10 years reliable answers to many of our present questions will be found.

Although it is not a direct objective, this training effort will to some extent alleviate the equally pressing problem of the shortage of practicing clinical anesthesiologists in the United States. An increase in the number of people attracted to the field is a natural result of the establishment of training programs which encourage the recognition and enhance the stature of the specialty.

INSTRUMENTATION RESEARCH

Mr. FOGARTY. Now, what is happening in the field of instrumentation?

Dr. POWELL. It is my understanding that a program report on the general areas of biomedical engineering and how it is expected to contribute to research has been prepared by the Division of Research Facilities and Resources and is being filed with the committee. The problems of instrumentation are intimately related to the special resources programs of that Division. They are also concerned with questions as to how far is it appropriate for NIH to support the development of detailed instrumentation activities, particularly as they approach fruition that might lead to commercial development and potentially to patents. We have a summary statement by Dr. Stone which we can furnish for the record.

(The statement follows:)

The present-day life scientist who is interested in phenomena at the macro-molecular and molecular levels is confronted with an acute dilemma. The former methods of observation of whole living organisms no longer suffice for the precise measurements needed now in molecular biology and biophysics. The need has developed for larger, more expensive, and more precise equipment. It is difficult for the individual scientist alone to justify the cost and sole use of a magnetic nuclear resonance apparatus, programmed gas chromatographs, a small reactor for biomedical research, X-ray crystallographic apparatus, an analytical centrifuge, or other expensive equipment running into the tens of thousands and often into hundreds of thousands of dollars.

Such a scientist is also confronted by another difficulty. The parameters of the experimental problem have expanded and new instruments are needed to measure the wider horizons. Special techniques must be developed to exploit recent advances in high-frequency physics, acoustics, light, and other areas in order to measure more accurately and more sensitively the structure of molecules and their arrangement in cells and tissues.

The medical scientist who is interested in the regulation of bodily processes which may lead to a new understanding of disease is confronted by a need to explore the science of engineering and apply the mathematics and principles of control system theory and information theory; for example, to the study of the biological control of blood pressure, to the invasive growth of cancer cells, or to the nervous control of respiration.

Each of the above examples of activity may be considered a part of a new and complex area where several sciences now focus and interreact. This complex field is now known as biomedical engineering. Instrumentation is a sophisticated part of this broad field which encompasses an area of development ranging from theoretical studies of mathematical models to the application of known physical instruments in biological systems.

A major program effort will be devoted to instrument development in which the knowledge gained in basic research will be applied in the design and construction of new energy transducers for the use of the life scientist. Also of importance is the provision of access to large and complex instrumentation needed by the scientist investigating a particular problem. This planned access will be provided through one or more special resource centers.

Examples of biomedical instrumentation development come easily to mind, the first of which has been supported by the Division of Research Facilities and Resources. High-frequency sound at the ultrasonic level was used and the problem of its focusing was first worked out on a theoretical basis by the biomedical laboratory I have in mind. These scientists then took this theoretical formulation and applied it in such a way that the visualization of these sound waves on a fluoroscope screen was possible in much the same fashion as X-ray examinations are made visible to the radiologist. This device was then applied in clinical medicine to the direct visualization of blood flow in organs without surgical intervention. A new important tool for the investigation of valvular lesions was thus discovered and developed. In addition to this example, I would like to point out that the development of rapid-scan ultraviolet densitometers, rapid photosynthetic process evaluation, magnetic flowmeters, and many other instruments now in common use would probably have taken place much quicker and with less problems for the scientist involved if a well-rounded program of instrumentation research and development had been available a few years ago.

At any time when a matter of patent right determination comes into question, we will be governed by the Department patent policy. This policy is now being studied and an announcement concerning it is expected in the near future.

BIOMEDICAL ENGINEERING CENTERS

Dr. SHANNON. I think what we are interested in, Mr. Chairman, is in establishing a limited number of biomedical engineering centers that will combine engineering physical science skills within an academic setting.

Mr. FOGARTY. Well, that is what I thought we were talking about a year ago. I thought some progress had been made along that line.

Dr. SHANNON. We have one at Northwestern University. We have applications for how many others?

Dr. STONE. Six applications in the house, sir, in various stages of consideration.

Dr. SHANNON. I would guess we would have others.

Mr. FOGARTY. This is a very important area, is it not?

Dr. SHANNON. Very important.

Mr. FOGARTY. That has not received enough consideration in the past. Our committee was impressed with the stapling machine that one of our outside witnesses showed us a couple of years ago that is used in heart operations or artery operations. He claimed that the original was practically stolen out of Russia and they refined it.

Dr. SHANNON. This is not an overstatement that it was done. It was done in the Bell Laboratories and the individual you have reference to is Mr. Stern.

Mr. FOGARTY. He is a retired contractor who had an interest in medicine and wanted to do something of value in the field.

Dr. SHANNON. The problem here is to have meaningful instrumentation developed to meet very real needs. Now, we have been approached in the past 5 years by most of the instrument development operations in industry, that have associated themselves with problems of telemetering in the Air Force or in the space programs or things of that sort. It is possible to contract with them for definitive instruments.

On the other hand, the big role that modern instrumentation has to play is its integration into research methodology so that the instrument evolves in response to a need that has developed as the research program proceeds from point to point. This cannot be done in a conventional industrial setting. It is because of this that we have

attempted to develop instruments, within a research setting, and this has probably been the only way to solve the problem of bringing modern instrumentation to the field of medicine.

GENETICS RESEARCH

Mr. FOGARTY. What are you doing in the area of genetics?

Dr. POWELL. We feel this is the most exciting field going forward at the moment. The Institute of General Medical Sciences in its research grant program has been instrumental in supporting several major activities in this field. For example, we number among our grantees predating the time of his Nobel Prize, Dr. James Dewey Watson of Harvard University, who has been a grantee of ours since 1957 and won the Nobel Prize this year. In this field, as you know, the major activities are dealing with the attempt, to use the expression, "crack the genetic code," to reach a full understanding of how genetic information is transmitted, and what is going on within the cells during this transmittal.

Mr. FOGARTY. Dr. Handler from Duke explained to us a year or two ago what this means but I must admit I didn't understand it. Would you try to get it in layman's language.

Dr. POWELL. Sir, I am not very sanguine about my capability of explaining this in a simple layman's fashion, either. Certainly not offhand. If you would like for us to attempt to prepare a report on this so that it would be more readily understandable, we would be glad to do so. Studies in this field incidentally are being conducted or supported by several of the institutes at NIH, and I am sure this will be reflected in later testimony.

Mr. FOGARTY. We will put such a report in the record, and see if you can get it in language we can understand.

(The report follows:)

THE PRIMARY GENETIC SUBSTANCES, RNA-DNA

Surveying the field of biology more than a generation ago, the British scientist, J. B. S. Haldane, made this prophetic observation: "The ultramicroscopic world which lies between the cell and the atom—it is there that our ignorance is the most profound. It is there that the outstanding problems of medicine will be solved. And it is there that discoveries will be made in the next century which will revolutionize medicine."

The validity of this prediction is apparent in the exciting developments now coming from laboratories where teams of scientists are unraveling one of the innermost mysteries of nature: the role of the nucleic acids, RNA (ribonucleic acid) and DNA (deoxyribonucleic acid) in protein synthesis. What we are learning about these substances—how they fit into genetics and how they affect life processes in organisms ranging from the single-cell amoeba to man—is already having and will continue to have a profound influence on the practice of medicine.

The importance attached to recent progress in this field is indicated by the fact that Nobel prizes in medicine for 1958, 1959, and 1962 went to eight scientists for their studies on the structure and function of RNA and DNA.

The interest of the scientific community and the significance it attaches to basic research in this field are reflected in the fact that the National Institutes of Health supports through research grants to universities and other research institutions more than 300 projects on various aspects of nucleic acid. Such support totals approximately \$9 million. In addition, the National Institutes of Health is conducting 35 research studies on the nucleic acids in its own laboratories in Bethesda.

BACKGROUND

Genetics may be broadly defined as the capacity of living material to maintain its specificity, or individuality, during proliferation. This definition covers the processes by which both single-celled organisms multiply and tissue cells proliferate, as well as the process by which a new individual is formed through the recombination of genes from two parent cells. Marked changes from the parent cells occasionally occur, which are in their turn perpetuated, and the result is hereditary modification. The term "mutation" is commonly applied to these occurrences.

The fundamental work which led to the discovery of the nucleic acids and their central role in genetics was performed by the Swiss biochemist Friederich Miescher, who is considered the founder of our knowledge of the chemistry of the cell nucleus. In 1868, he isolated nuclei from pus cells, and demonstrated that they contained an unusual phosphorus compound. A few years later he described an acidic compound that he obtained from salmon sperm heads; this compound came to be recognized as nucleic acid. These investigations were followed by others, and by the 1890's it was known that nucleic acids were present in all cells and tissues.

Interest in this area subsided for a time, with the exception of a flurry of investigations around the 1920's, but it was not until the 1940's that these substances began to be identified with the mechanisms of heredity. Two milestones of progress in this direction stand out:

1. The discovery by Oswald Avery, Colin MacLeod and Maclyn MacCarty of the Rockefeller Institute for Medical Research, in 1944, that DNA from one type of pneumococcus can be incorporated into a second pneumococcus type, and can convert the latter into the type from which the DNA source was derived. This and subsequent work led to the realization that DNA is the primary genetic substance of all cellular organisms.

2. The construction by James Watson of Harvard University and F. H. C. Crick of Cambridge University, in 1953, of a molecular model of DNA, which now appears to be established, and which offers the best explanation available of the mechanism of transfer of genetic characteristics.

Other vital discoveries concern the structure and function of RNA which, in contrast to DNA, is not confined to the chromosomal elements of the cells but is spread throughout the nuclear and cell plasm. RNA is also known to carry genetic information.

NIH SUPPORT

The National Institutes of Health has long maintained an active interest in the development of knowledge concerning the nucleic acids and their role in genetics. Watson, who with Crick received the 1962 Nobel Prize for his work in elucidating the structure of DNA, has been a grantee of the National Institute of General Medical Sciences (formerly the Division of General Medical Sciences) since 1957. In addition, extensive research training programs have been maintained to assure a continuing supply of able basic research scientists to pursue investigations in this as in other areas. Basic research in specifically oriented aspects of genetics is being conducted under the auspices of the other institutes at NIH as well, notably arthritis and metabolic diseases, cancer, neurological diseases and blindness, and allergy and infectious diseases. This reflects the fundamental place of genetics in the life sciences.

RESEARCH KNOWLEDGE

The building blocks of either RNA or DNA are: a pyrimidine or purine base; a pentose or 5-carbon sugar (ribose or deoxyribose); and phosphate. The pyrimidine or purine combination with pentose forms a nucleoside; the addition of phosphate forms a nucleotide; a chain of nucleotides, or polynucleotide, ultimately forms the nucleic acid. Thus, nucleic acids are long chains of nucleotides.

The characteristic of RNA is that its nucleotides contain the purines adenine and guanine, the pyrimidines cytosine and uracil, the pentose ribose (from which the nucleic acid derives its name), and phosphate. DNA contains the same purines, the pyrimidines cytosine and thymine, deoxyribose, and phosphate. Some variations in one or more of the foregoing components are known to occur along various nucleic acid chains.

The arrangement of nucleotides along the chain, and the spatial configuration of the chain, determine the properties of the nucleic acids. In the Watson-Crick model for DNA, the nucleotide chains are represented as two strands twisted around each other like a pair of winding staircases and cross-linked to each other by hydrogen bonds. RNA apparently occurs in single long chains (some theories hold that it may occur as a 2-stranded helix) in structures called ribosomes, and in smaller units which may be soluble—the so-called transfer RNA. They act as coded “memory units,” along the lines of data-processing devices. In cellular organisms, it is considered that RNA, deriving “instructions” from DNA, directs the synthesis of specific proteins by activating and linking amino acids into specific sequences characteristic of the protein.

The nucleic acids are relatively unreactive by comparison with proteins. Perhaps for this reason they have survived during the evolutionary process to record and transmit the successful experiments of evolution. Their role is the maintenance of the cellular machinery for making the cell's protein, some of which are enzymes. These, in turn, interact with other molecules to produce the multiplicity of substances found in cells and lead to the complex series of reactions which are referred to as cellular metabolism or, in social terminology, life.

A mutation in a small segment of the DNA chain may result in a change in the amino acid composition of a protein, and a corresponding alteration in the metabolic processes of the cell. Some organisms, in particular plant viruses, contain only RNA, which performs the functions of genetic transfer with similar potentials for mutation.

The foregoing description is, of course, highly simplified. While much is known about the structure and energies involved in the activities of DNA and RNA, much more needs to be learned before it can be said that a breakthrough has been made in solving the genetic code.

The recent announcement of a new development in electron microscopy by Dr. A. P. Wilska at the University of Arizona may enable science to take the next forward step in resolving the structure and function of molecules such as DNA and RNA. With this new development, it may be anticipated that the resolving power of the electron microscope may be extended beyond the limit of 6 to 8 Angstroms, down to the order of interatomic packing distances. (An Angstrom is one ten-millionth of a millimeter, or a 250,000,000 part of an inch).

RESEARCH NEEDS

Much more work needs to be done to elucidate the structure and mechanisms of action of the nucleic acids. The synthesis by Nobelist S. Ochoa of New York University and others of polynucleotides (the basic RNA units) has altered the pace of structural studies of this nucleic acid. Studies along these lines are being pursued at the National Institutes of Health.

Among the questions which remain unanswered are these:

1. What makes the code in one original cell, the fertilized egg, vary so precisely and sequentially in the construction of the many types of cells in a complex organism?
2. How does the cell administer the overall activity of its complex machinery?
3. What turns this mechanism on and off at certain intervals in the life of the organism?
4. How does the control process break down in malignant cells?

Investigations continue to be pressed at the National Institutes of Health and in other laboratories in broad and intensive programs to find answers to these and related questions. Bit by bit, evidence is being uncovered as to the manner in which DNA, RNA, and proteins perform their functions, and on regulatory mechanisms that operate in the unfolding of their activities. With each forward step in knowledge accrued from basic research in these areas, new insights are gained in the fundamental life processes as they determine health and disease. Progress will come as a result of contributions from scientists representing many disciplines in the biological and physical sciences, because it is the nature of all sciences to have a convergent interest: the enhancement of human well-being.

Basic research in genetics opens the prospect of new insights into many conditions that have puzzled and frustrated physicians and biologists. Genetics, being fundamental to the understanding of the total metabolic process of the

living organism, provides an important key to the ultimate control of many disorders of development and of other life processes.

Among the areas reaping the benefits from research in basic genetic phenomena are: developmental defects, cancer, viral and other infectious diseases, blood dyscrasias, endocrine disorders, idiosyncrasy to drug action, mental disease, enzyme deficiencies, allergy and immunity, problems in organ transplantation, radiology, and a long list of aberrations which has been designated as inborn errors of metabolism.

For the scientists who are charting the biochemistry and biophysics of genetics, this field is the most challenging and exciting frontier in the biological sciences—and the key to its understanding is knowledge of the role played by the nucleic acids, DNA and RNA.

STRUCTURE OF NUCLEIC ACIDS

Dr. SHANNON. I have an analogy I think might clarify the situation. The nucleic acid that carries this information that determines the developmental potentialities of a line of cells is a complex protein molecule, the structure of which varies in minor detail from one species to another or from one individual to another.

I think if you could liken this to an IBM machine card where the placement of the specific holes across the card or up and down the card permits one to catalog a great deal of information on a very small piece of space, and then use this for sorting or for actually reproducing other IBM cards that are not precisely the same as the initial one. If one can view the placement of the holes on an IBM card, we will say on a given line as being roughly equivalent to the placement of specific chemical components of this large molecule in space and the placement on the IBM card in terms of the line, each line representing a different character or different characteristic. So that the qualitative components that composed the card, that is the number of lines that were filled out and their placement across the card, permit the type of cellularization of information that carries a very meaningful message.

One can say that the nucleic acid that carries this information basically is no different in concept than an IBM card which carries information of a somewhat analogous size.

For instance, if you take an IBM card and very simply describe a man in terms of his height, his weight, his sex, his age, his origin, disease background and disease susceptibility, a whole host of characteristics, and these small subcellular particles we call nucleic acids carry comparable information of that sort, characteristics of the individual difficult to understand, as normal life expectancy, his tendency to age, his susceptibility to specific groups of diseases, together with such mundane things as the color of his eyes, the color of his hair, his tendency to be tall, to be short, to be fat, to be thin, all of this is contained in coded fashion on this subcellular equivalent of an IBM card. The body has a mechanism that is roughly equivalent to an IBM sorting or reproducing machine.

I heard a very interesting discussion by some of the people from Bell Laboratories on miniaturization of electronic equipment. They pointed out there is scarcely any discrete operation within a cell in the central nervous system to be analogized which cannot be developed electrically and portrayed by circuits; that the difficult thing for their engineers, their physicists, scientists to understand is how the capa-

bilities of an electrical machine which is very large in size which can do a job, can be compressed into a biological entity of such sub-microscopic size.

This is the detail, the mystery. It is not that a thing can be done, but it is how it can be done and the mechanics of its being done in these subcellular, submicroscopic forms.

DEFINITION OF DNA

Mr. FOGARTY. When you told us about this last year, you referred to a material designated by three letters.

Dr. TERRY. You mean, were the initials used like DNA?

Mr. FOGARTY. I think so.

Dr. POWELL. DNA, sir, is the term for the nucleic acid material to which Dr. Shannon referred.

There are two most critical things that have been determined recently, or at least partially determined. First is that DNA is basically the same material, irrespective of what animal or what genetic determination is at hand; that is, irrespective of the species involved or whether it is eye color or height being determined. The arrangement of the molecules and the substances within the molecules make the difference and pass along the "key."

REPLICATION OF GENETIC MATERIAL

The second prime issue is the very interesting question as to how genetic material replicates itself; how it reproduces itself from the original two cells, which combine to start the reproductive process, on through to all the cells of a complete human being, meanwhile maintaining the complete code of genetic information. This code is carried in every cell in our bodies.

This has not been fully worked out, but certain interesting points have developed. Apparently it is a matter of this material, as it were, splitting lengthwise in the middle; having split lengthwise in the middle, it leaves hills and valleys, which are filled in by formation of a "mirror image." The filled-in material can then split again into pieces identical to those formed by the first split.

I do not think we are prepared, at this point, to say why the replicating goes forward.

I might add that the reason I was a little hesitant to attempt the full explanation is that one of the most lucid explanations I have ever heard of this subject was the one given by Dr. George Beadle, an internationally known geneticist now president at the University of Chicago, at the dedication of the Kennedy Foundation Laboratories.

As I remember, you were also at that luncheon, Mr. Fogarty.

I remember the difficulty that he had in making it understandable to the layman, because it is a rather deep and technical subject.

ORGAN TRANSPLANTS

Mr. FOGARTY. It sure is, as far as I am concerned.

What are you doing in the area of organ transplants?

Dr. POWELL. The question of organ transplantation is not one primarily of developing technical capabilities to remove organs or change them from one animal or individual to another. Rather it is a prob-

lem of getting a "take"—that is, to have the organ remain viable and functioning after it is transplanted.

This is because of the defense mechanism one's body builds up against any foreign substance. We can successfully transplant skin or whole organs from one animal to another when these animals are the genetic equivalent of identical twins—that is, purebred strains of animals. Organ transplantation in twins is not an insoluble problem. The real difficulty we face is to develop a more thorough understanding of the basis of the body's immunology, its defense mechanisms.

Mr. FOGARTY. You are talking about something like transplanting kidneys?

Dr. POWELL. Yes, sir. I assumed that was your question.

Mr. FOGARTY. Yes. That was one of the things I had in mind. I know in Boston they have been doing these operations.

Dr. POWELL. Yes, sir.

Mr. FOGARTY. I noticed in the paper a few weeks ago some girl from a Midwestern State offered one of hers to someone in the hospital who was no relation. I just saw the picture of the two of them in the paper the other day and both apparently are doing fine right now.

Dr. POWELL. Yes, sir. I saw reference to what I believe is the same case.

The situation here is that, just as our defense against disease takes time to develop, so the body takes some time to decide whether to reject the transplanted organ. One is quite uncertain, until there has been a passage of many months, whether an organ transplantation will be successful.

Mr. FOGARTY. Some of the twin operations have not been successful either, have they?

Dr. POWELL. Some of them have not, but certainly some of them have.

Mr. FOGARTY. Yes.

Dr. POWELL. There appears to be no insurmountable problem to the transplantation of organs in twins. However, we are at this point concentrating our program activities on studies which we hope will lead to an understanding of why the immunological process acts the way it does, and on developing ways in which the body's natural tendency to throw off an organ from someone else might, perhaps, be thwarted on a selective basis. This defense mechanism can be thwarted, but unfortunately when it is using currently available techniques, the defense mechanism against infectious organisms is also thwarted. This, of course, does not lead to a successful result.

Mr. FOGARTY. Are you doing any work in this area with germ-free animals?

Dr. POWELL. Work is going forward with germ-free animals, because they are experimental subjects which have a quite different status in terms of both the defense mechanisms that have already been built up, and the ability to develop new immunological defenses.

Mr. FOGARTY. Are they more successful, these transplants, in germ-free animals than the ordinary animal?

Dr. POWELL. They have not been significantly more successful. There have been some attempts and the information at this point, as is very often the case in early stages of research, is somewhat equivocal.

Mr. FOGARTY. Is there any other example you would like to give on transplants?

Dr. POWELL. No, sir.

Mr. FOGARTY. Mr. Denton.

COMPARATIVE TRANSFERS

Mr. DENTON. The amount of money that has been transferred from this agency to other agencies is rather significant. I would like to put in pages 10 and 11 of the justifications that illustrates that.

(The pages follow:)

Explanation of transfers

	1963 estimate	1964 estimate	Purpose
Comparative transfer to— “Chronic diseases and health of the aged”.	-\$125,000	-----	To provide for centralization of chronic diseases research grants and related review and approval costs within the Bureau of State Services.
“Communicable disease activities.”	-88,000	-----	To provide for centralization of communicable diseases research grants and related review and approval costs within the Bureau of State Services.
“Community health practice and research.”	-1,883,000	-----	To provide for centralization of community health research grants and related review and approval costs within the Bureau of State Services.
“Nursing services and re- sources.”	-2,443,000	-----	To provide for centralization of nursing research grants, fellowships and training grants, and related review and approval costs, within the Bureau of State Services.
“Environmental health sci- ences.”	-1,479,000	-----	To provide for centralization of environmental health training grants within the Bureau of State Services.
“Biologic standards”-----	-3,947,000	-----	To establish a separate appropriation for the Division of Biologics Standards.
Comparative transfer from—“Nati- onal Heart Institute.”	+\$5,120,000	-----	Transfer of the primate center program to the General Research and Services, NIH appropriation, Division of Research Facilities and Resources.
Transfer to—“Operating expenses, Public Buildings Service,” Gen- eral Services Administration (76 Stat. 728).	-85,000	-----	Transfer of rental costs to GSA.

SOURCE OF ADDITIONAL EMPLOYEES

Mr. DENTON. I have difficulty, Mr. Kelly, about your number of employees. I notice that you are asking for 79 additional employees. But on page 4, if you will take the Office of Research Grants, you show in 1963 that you had 20. In 1964, you want 72, which is an increase of 52. Then if you turn to page 5, you will see you show international research in 1963 had no employees, and that you are asking for 62 for 1964, which increases 62.

How do you reconcile those two?

Mr. SEGGER. Mr. Denton, the bulk of the direct operations of this activity was carried this year in another part of the budget—in the management fund—and so the figure shown in this table is not comparable to the figure we show in 1964 under this account.

Mr. DENTON. Which figure is not comparable?

Mr. SEGCEL. The 20 positions in 1963 are only those positions which were provided in this appropriation when it was approved last year.

The 52 other positions which were carried in another part of the budget for 1963 are not shown on a comparative basis to the 1964 request in this account.

Mr. DENTON. I do not understand that.

Mr. KELLY. May I reconcile the figures, sir?

Mr. DENTON. Yes, sir.

Mr. KELLY. Look on page 4 where we show 20 and 72 for an increase of 52, that corresponds with 2 figures that appear on page 5 in 1963; 0 for international research and 20 for training activities. However, the difference of 52 is carried in another part of the budget—the management fund.

Is that not correct?

Mr. SEGCEL. That is right.

Mr. KELLY. And in 1964, it shows 62 for international research and 10 for training, for a total of 72. Then this shows an increase of 62.

Mr. DENTON. Where do you get the total of 72?

Mr. KELLY. Sixty-two for international research and 10 for training activities relates to the total of 72 appearing on the preceding page.

Mr. DENTON. As I get it, the 20 on page 4 were in training last year.

Mr. KELLY. That is correct, sir.

Mr. DENTON. And you are transferring 10 of them to the Office of International Research?

Mr. KELLY. That is correct, sir.

Mr. DENTON. Now, you are also adding 62 people to the international research.

Mr. KELLY. It is a net increase of 62; 62 less than 10 in this appropriation, but not a net increase of 52.

Mr. DENTON. Pardon me if I am a little confused with these figures, but let's take the 52 first. Where did those 52 come from?

Dr. SHANNON. Could we go back and let me give you some qualitative statements first and then let me hang some numbers on top of them.

The Office of International Research was set up about 2½ years ago as a straightforward, simple staff function to advise my office on certain activities that relate to the international field.

As that Office has become organized, we have added functions to it by transferring them from other areas in order to pull the totality of our international activities into a single office. So that these numbers have changed over the past 3 years and it is not until this budget that they are totally pulled together.

The figure of 72, you see now, are those individuals who actually are related to the activities now and will continue to be related to it next year.

Mr. DENTON. Now, 10 of those came from training. Where did the other 62 come from?

Dr. CUMMINGS. No, sir. May I try to clarify this.

I think there is some confusion here on the 10 positions related to training. We have this fiscal year 62 positions in the international program and project the same number for the next year.

The Congress appropriated funds last year to establish an international research associate program, which is for training young doctors and scientists for assignment out of the country. These 10 trainees are charged to my office, which administers the program, but in fact are young scientists and physicians who will be working abroad.

I believe this would give us the figure of 72. That is confusing.

Mr. DENTON. All right, now, the 62 that you had, did they come from some other agency or are they new employees?

Dr. CUMMINGS. Sir, some of them have been recruited from outside NIH. Many of them have been employees within the agency and have been brought to the Office of International Research with the programs that fit into the international area.

Mr. DENTON. Now, as you transferred them over to this department, were they taken away from the other one?

Mr. KELLY. Yes, sir. I have here the second volume of the National Institutes of Health and under the "Management fund," it shows that the program direction area was decreased by 62 positions. It is reflected here as a transfer of \$1,012,000 from the management fund to the general research and services for international research.

Mr. DENTON. You mean 62 were in management before?

Mr. KELLY. No, they were part of the management fund, which, as you know, is supported by all of the institutes to provide program direction.

Mr. DENTON. In what agency did they work?

Dr. SHANNON. NIH.

Mr. DENTON. What division, Heart, Cancer, or General Medicine, or what?

Dr. SHANNON. They worked with Dr. Cummings. But initially his activity was supported within the management fund to which all the institutes contribute a part of this support. This is a central funding of an activity that supports the activity of all the institutes.

Now, for the first time, what we have done here is to have them broken out, to break all of those positions out and to present them as an entity in itself, and associate them with the function they perform.

Mr. DENTON. Now, you have taken them from the management appropriation and placed them in this, that is the 62?

Dr. SHANNON. Yes, sir.

Mr. KELLY. Yes, sir.

Dr. SHANNON. We have taken the dollars, we have taken the positions. This does not represent an expansion, by even one, of the number of individuals.

Mr. DENTON. Yes. Now, were these men carried under the management fund, these 62 men?

Dr. SHANNON. Yes, sir.

Dr. TERRY. Actually doing the same thing they will be doing.

NUMBER OF EMPLOYEES IN FOREIGN COUNTRIES

Mr. DENTON. These men will be working in foreign countries?

Dr. CUMMINGS. Sir, they split roughly 60-40 percent. We have in addition to the scientists actually doing research abroad charged to my office a series of oversea science offices to provide scientific intelligence and data to the NIH study sections and councils which review foreign applications. About 37 of these positions are for personnel working abroad. The remainder are in the NIH central structure where we do overall foreign program analysis and planning, as well as administering a series of international activities.

Mr. DENTON. They are paid out of the different funds, different categorical agencies, like Heart, Cancer, and so forth, for the different grants; is that right?

Dr. CUMMINGS. In the past, sir, they were paid by the management fund in the Office of Director. We are proposing that next year they appear in the budget we have before us.

FUNDING OVERSEA INVESTIGATIONS

Mr. DENTON. How do you fund these grants you have for oversea investigation?

Dr. CUMMINGS. The research grants are funded by the individual institute with a categorical interest in that particular research problem.

USE OF COUNTERPART FUNDS

Mr. DENTON. Yes. And is it drawn on the Treasury of the United States?

Dr. CUMMINGS. Yes, sir.

Mr. KELLY. We have a policy to the extent that there are foreign currencies available and to the extent that they could be used to carry on a project, that they be used; that we purchase them with our American dollars.

Mr. DENTON. Would it not be better to pay them direct with counterpart funds or 480 funds?

Dr. CUMMINGS. We do wherever they are available to us. Last year 12 percent of the research grant funds awarded abroad were paid in foreign currencies. This occurs in those countries where there are excess currencies.

Mr. DENTON. Only 12 percent?

Dr. CUMMINGS. Yes, sir. In some countries 95 percent of all grants were paid in foreign currency. However, these funds are not available in many countries.

Mr. DENTON. Why would it not be better to give us credit on this from money we get out of counterpart funds and 480 funds and do it just like you do with the special foreign currency programs?

Mr. KELLY. I think that there is a difference. In the foreign currency program, we are identifying the availability of foreign currency and the availability of research possibilities in those countries.

Here we are anticipating that the funds will be used for specific purposes of heart, cancer, and so forth, but it may develop that this can be done in a foreign country.

Mr. DENTON. I do not see, if it is done for cancer, heart trouble, and so forth, why you should not use those foreign funds.

Mr. KELLY. We are using it to the extent we can.

Mr. DENTON. Just the same as foreign exchange?

Mr. FOGARTY. Am I correct; you are talking about using dollars when you do not have foreign funds available?

Mr. KELLY. If we go into the country where the funds are available, we are using them. If we go into a country where the moneys are not available, we use our regular appropriations.

Mr. DENTON. Of course, there are a few countries where you would not find some funds, U.S. funds; but I think most of these you mentioned you will find funds available.

Mr. KELLY. When I say "available," I should have said where the Treasury Department has certified them to be excess to the needs.

Mr. FOGARTY. You see, all the Scandinavian countries or Germany, France, or Great Britain, would not have any counterpart funds.

Dr. CUMMINGS. I have a brief report of our utilization of excess foreign currencies if you would like that introduced in the record. It shows in fact those countries where these funds were available to us and how we applied them in payment of our awards.

Mr. DENTON. All right. Thank you.

(The report follows:)

USE OF U.S.-OWNED FOREIGN CURRENCIES IN PAYMENT OF FOREIGN GRANTS

In line with the President's policy for the reduction of dollar expenditures abroad, NIH has since January 1961 been paying all foreign research and training grants in foreign currencies wherever U.S.-owned currencies are available for this purpose. NIH policy authorizes payment in U.S. dollars of the portion of such grants which cover equipment and supply purchases or publication costs in the United States.

During fiscal year 1962, U.S.-owned foreign currencies were available in only 7 of the 49 foreign countries where NIH grants were located. These countries were Israel, Netherlands, India, Jordan, Spain, Turkey, and Yugoslavia. Excess U.S.-owned foreign currencies were not available for NIH payments in Canada, the United Kingdom, Sweden, Japan, France, Australia, and Italy. These countries, together with Israel and Netherlands, contribute most toward U.S. medical research objectives, and, therefore, about two-thirds of NIH grant payments are made in these countries.

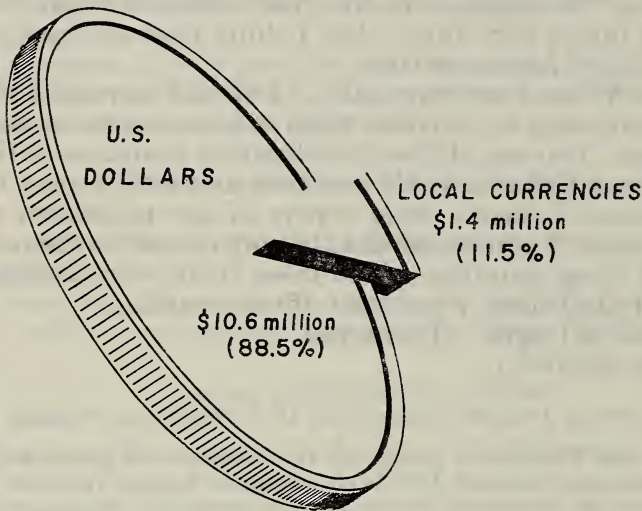
Altogether, research grant payments in local currencies amounted to \$1,419,378 or 11.5 percent of the total awarded. However, in countries where excess foreign currencies were available, local currencies made up 91 percent of the total amount awarded. As indicated in the attached chart, this overall result comes about largely because awards in Israel and the Netherlands were paid almost wholly in local currency.

The use of foreign currencies for payment of research grants does not lessen the need for appropriated dollar funds. NIH must in effect reimburse the Treasury from appropriated funds for the excess U.S.-owned local currencies used to make research grant payments in foreign currencies. This is true also of local currency derived from sales abroad of U.S. agricultural surpluses used to finance the cost of NIH collaborative research agreements in foreign countries under section 104(k) of Public Law 480.

Attachment: Chart.

Public Health Service - NATIONAL INSTITUTES OF HEALTH

*APPROXIMATELY 12 PERCENT OF THE FUNDS AWARDED
TO FOREIGN INSTITUTIONS FOR RESEARCH GRANTS
IN FY 1962 WAS PAID IN U.S. OWNED LOCAL CURRENCIES*



*EXCESS U.S. OWNED LOCAL CURRENCIES WERE
AVAILABLE FOR NIH RESEARCH GRANT PAYMENTS
IN ONLY 7 COUNTRIES DURING FY 1962*

<u>COUNTRY</u>	<u>TOTAL AMOUNT</u>	<u>AWARDED IN LOCAL CURRENCY</u>	
	<u>AWARDED</u>	<u>AMOUNT</u>	<u>PERCENT</u>
India	\$ 54,646	\$ 43,796	80.1
Israel	951,466	909,013	95.5
Jordan	54,489	54,489	100.0
Netherlands	148,324	144,949	97.7
Spain	13,680	13,680	100.0
Turkey	9,200	9,200	100.0
Yugoslavia	32,000	7,000	21.9
Int'l Organizations in above countries	295,584	237,251	80.3

Office of International Research
Program Analysis Section
Feb. 11, 1963

OBLIGATION OF INSTITUTE'S FUNDS

Mr. DENTON. Now, did I understand from the statement in answer to Mr. Fogarty's question that of the funds available for research by the National Institute of General Medicine, that all of that has been obligated except the sum of \$332,000?

Dr. SHANNON. No, the estimate is, sir, that by the end of the year, the funds that are available will have been expended save \$332,000 that is put in research.

Mr. DENTON. How much is obligated as of today?

Dr. SHANNON. Roughly I would say about 35 or 40 percent. We have been through two of a cycle of three councils in relation to obligation, and they break down in that the June council that takes the initial action for the fiscal year—

Mr. DENTON. That is the last one?

Dr. SHANNON. This is the first one. In June, in anticipation of the next year's expenditure, the amount of business conducted is larger than the other two.

The last round of councils is just beginning to start this week. We will have obligated at the present time approximately 70 percent of those. We have been through the June, we have been through the October and November series; the last series of council meetings is just about to start.

Mr. DENTON. Is there any carryover?

Dr. SHANNON. No; no, sir.

RATING SYSTEM FOR RESEARCH GRANT APPLICATIONS

Mr. DENTON. Now, the Division of Research Grants rated these grants that come to you?

Dr. SHANNON. No, sir. The applications are rated first by study sections.

Mr. DENTON. How do they rate them, 1, 2, 3, 4; A, B, C; or just what system do they have of rating?

Dr. SHANNON. The system is as follows. The first action is one of approval or disapproval, that is to decide whether to recommend payment or not to recommend payment. Then those where payment is to be recommended, the individual study section members rate them in terms of their estimate of relative excellence in a series of numbers, 1 through 5. These numbers are then added up, divided, and multiplied by 100 to give the rate. For instance, to take an example, we will say the rating was by 10 people: 5 gave a rating of 1, 5 gave a rating of 2. The average of that would be $1\frac{1}{2}$. So the average priority would be 150. This is to get a large number to work with, simpler without using decimals.

The rating then of any project can be from the most excellent that warrants support, which would be 100, to the least excellent that warrants support, which might be 500.

GRANTS AWAITING ACTION

Mr. DENTON. Yes, I see. Now could you put in the record the grants that are awaiting action?

Dr. SHANNON. Yes, sir.

Mr. DENTON. In the categories 1 through 500.

Dr. SHANNON. Yes, sir.

(The information follows:)

Research grants for 1963 support awaiting action in the March 1963 advisory councils¹—Grants recommended for approval are listed in priority ranges

[Amounts in thousands]

Recommendations of study sections													
Disapprovals		Approvals								Total awaiting action			
		100 to 199		200 to 299		300 to 399		400 to 500					Subtotal, approvals
Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount
140	\$9,390	74	\$3,812	148	\$4,481	56	\$2,157	5	\$74	283	\$10,524	423	\$19,914
129	3,645	22	1,118	69	1,987	42	1,304	5	63	138	4,472	267	8,117
129	15,710	60	2,920	135	4,720	90	3,035	15	560	300	11,235	715	26,945
155	4,311	31	1,235	99	2,611	54	1,110	12	158	196	5,114	351	9,425
23	819	21	208	21	776	20	370	3	31	53	1,385	76	2,204
154	4,018	55	2,146	129	2,951	82	1,397	3	57	269	6,551	423	10,569
89	2,836	76	2,538	103	1,898	39	606	4	34	222	5,076	311	7,912
86	3,188	44	1,522	86	1,881	33	731	4	79	167	4,213	253	7,401
1,191	43,917	372	15,499	790	21,305	416	10,710	50	1,056	1,628	48,570	2,819	92,487
Total-----													

¹ This table excludes applications for 1964 support, applications to be deferred for future councils, and recommended disapproved amounts of approved grants.

Mr. DENTON. Off the record.
(Discussion off the record.)

SPECIAL REVIEW OF LOW-RATED GRANT APPLICATIONS

Dr. SHANNON. The Biological Study Section could not have a large number of grants. They might in a single round view as few as 20 or 25 grants in a single sitting.

When you get to small numbers like that, all of those grants may be extraordinarily excellent, but the lower 10 percent still will be subject to special review.

Now, our staff will take a look at those lower 10 that might have, in the case of biophysics, a distribution like this, where the lower 10 percent will be in the cutoff range around 200 to 250.

Now, our staff will take those grants and present them to the Council, and with the estimate that while this is in the lower 10 percent and, by their criteria, must receive separate consideration, nonetheless on the study of these, in comparison with all other grants, in the general ranking of all other grants, these should not be considered marginal or suspect and should be given full support. On the other hand, in cardiovascular, in the Cardiovascular Study Section that may have a larger number of grants where the lower 10 percent does come in the range, say, of priorities 400 to 500—in this case the executive secretary might well say that this individual who has a low priority has a wholly new approach to the solution to a problem of great relevance in the cardiovascular field. We feel the Council should give consideration whether or not one should award risk capital in exploring this whole new idea, this unconventional but promising new lead. This is a young investigator, so that staff might recommend that he be supported perhaps at a somewhat lesser amount but perhaps for a shorter period of time than the individual wants. Then this recommendation goes up in parallel with the Study Section recommendation for consideration by the Council.

Mr. DENTON. Let me see if I understand you. Ordinarily you would make the grants in accordance with their ratings.

Dr. SHANNON. Yes, sir.

Mr. DENTON. But if there are special circumstances in that there are very few projects in a particular field, you might think it advisable and the committee might decide to grant one even though it may have a rather low rating?

Dr. SHANNON. That is right, low relative rating, but definitely within the group evaluated as worthy of support by the Study Section.

Mr. DENTON. Low relative rating. Because of the importance of the investigation in that particular field?

Dr. SHANNON. Yes, sir.

Mr. DENTON. Is that about right?

Dr. SHANNON. That is correct, sir.

Dr. TERRY. But all of these, Mr. Denton, are projects which the study sections have characterized as worthy of support in their opinion.

Mr. DENTON. Yes.

Dr. TERRY. It is a relative thing within the category of approvable grants.

Mr. DENTON. Now, practically all of your research in this agency is in the field of general medical science?

Dr. SHANNON. In this particular appropriation, yes, sir.

Mr. DENTON. And the appropriations for the Office of International Research and the Division of Research Facilities and Resources come from other appropriations.

Dr. SHANNON. No, sir. The Office of International Research here, the cost of running the activity, the cost of carrying the international centers, the cost of carrying the international research program and the like are contained in this appropriation.

Mr. DENTON. Yes.

Dr. SHANNON. But over and above that, the cost of support of substantive programs of research by the grant mechanism, these are contained in the categorical programs.

Now, this in part stems from the fact that our basic authority permits us to utilize such results as do occur in the international field to further our categorical objectives. So that we feel that if a cancer research project is supported, it should be supported by the Cancer Institute; if a heart research project is supported, it should be supported by the Heart Institute.

REDUCED APPROPRIATION FOR FACILITIES

Mr. DENTON. How were you able to reduce this appropriation for research facilities and resources by \$4,846,000?

Dr. SHANNON. Do you want to comment on that, Dr. Stone?

Dr. STONE. I will answer this, sir. The \$4,846,000, to which you refer, results from a decrease in the general clinical research centers programs and slight increases in other programs. The net result is, as you reported, \$4,846,000.

It was felt during the budget review that the appropriation could be reduced without it substantially diminishing the quality and spread of the program of general research, general clinical research centers, by the amount I mentioned.

Mr. DENTON. Now, you do practically no intramural research in this Institute?

Dr. SHANNON. None, sir.

DUTIES OF NEW PERSONNEL

Mr. DENTON. Where you show that you have an increase of 79 employees, you really have no increase; is that right?

How much is the actual increase? Take 62 away from management, you are taking 10 away from training.

Mr. SEGGER. Twenty-seven positions is the net increase.

Mr. DENTON. Where are they?

Mr. SEGGER. They are in the review and approval. In other words, the administration of grants activities.

Mr. DENTON. Why do you need 20 extra ones there?

Dr. SHANNON. Because these run roughly parallel to the size of the dollar expenditure in the grant area.

Mr. DENTON. I think that is all.

EXCESS FUNDS RETURNED TO TREASURY

Mr. LESINSKI. Dr. Shannon, when the chair was questioning you about funds and you mentioned that we purposely have allocated additional funds, more than necessary, in case of emergency, and that the chairman mentioned the fact if you have any surplus funds to turn them back to the Federal Treasury; have you ever turned back any excess funds to the Federal Treasury?

Dr. SHANNON. Oh, yes, sir.

Mr. LESINSKI. How often?

Dr. SHANNON. Each year for the past 3 years. I do not have the precise figures, but substantial amounts. We would be glad to furnish these.

(The information follows:)

Unobligated balances from operating appropriations of National Institutes of Health

Fiscal year :	Amount
1960-----	\$9, 650, 000
1961-----	13, 692, 000
1962-----	70, 580, 000

Dr. TERRY. As an example, Mr. Lesinski, I believe in 1962, at the end of fiscal year 1962, we turned back approximately \$23 million.

Mr. KELLY. We anticipate we will turn back approximately \$25 million this year.

Mr. LESINSKI. So the committee has been giving you too much money; is that it?

Mr. KELLY. I think that it should really be put on the basis that in certain categories, it has developed that there have not been the opportunities and, despite the availability of funds, it has not changed the concept that they will not be used unless there is an opportunity for scientific excellence.

Dr. Shannon also pointed out the problem that there is a difficulty in watching a program when you do not have your final decisions made until October or November as to how much money is available.

Dr. TERRY. Frankly I think this is a splendid example of responsible management, where we have the guts to turn it back to the Treasury because we cannot spend it wisely.

END-OF-YEAR EMPLOYMENT

Mr. LESINSKI. I appreciate that. I think it is commendable. On the other hand, Mr. Denton has constantly been pointing out the increases in the latter part of the fiscal year. Is it due to the fact you have your review in June for the succeeding fiscal year? Is that the reason why you put additional employees on the staff at that time, according to your records?

Dr. SHANNON. No.

Mr. LESINSKI. Through the various statements, it has been mentioned that you have an average number of employees during the year, then you have a mean number of employees, then you have a maximum number of employees. At the end of the fiscal year, you usually have the maximum number. Is it a fact you review in June for the various

project grants and that is the reason you have more employment then?

Dr. SHANNON. No, sir; I do not think so. I think our end-of-year employment is higher than our mean or beginning employment because we have been in a period of expansion, and the mechanics of our budget or the availability of funds, as has been emphasized before, are such that in general we are not given a clear signal to go ahead until October or November. We must then recruit and develop a program largely in the last 6 months of the fiscal year, rather than in the first 6 months of the fiscal year.

This affects our capability of developing programs, it affects the pattern of our employment of persons, it affects the pattern of our expenditure of funds.

Now I will say that it is unusual for us to have had our apportionment request acted upon and handled by the Bureau of the Budget within the first quarter of the year.

Mr. LESINSKI. No; in response to Mr. Denton as to review of grants, you said it was done in June; did you not?

Dr. SHANNON. No, sir.

Mr. KELLY. One of the councils.

Mr. LESINSKI. One of the councils?

Dr. SHANNON. June, October–November, February–March.

Mr. LESINSKI. But the council meets in June?

Mr. KELLY. It has three meetings.

Mr. LESINSKI. That is correct. I know that. But the point is you also say that you have the largest number for review when the council meets in June.

Dr. SHANNON. I would say it is about 40, then 30–30 for the other two periods.

Mr. LESINSKI. It has no bearing upon whether you have more employment, then, in June?

Dr. SHANNON. No, sir; it is purely due to the mechanics of funds available within appropriations and to the employment of students during the summer months.

Mr. KELLY. I think, Mr. Lesinski, that this is probably the best example we have of all of the cases that we have discussed of why the June employment should be higher.

You have, in the one hand, as Dr. Shannon has indicated, a growing organization, and it is building toward that growth. You also have the opportunity of getting the best recruitment of young college graduates at the end of the scholastic year. You have the third problem that is associated with having a sizable program of summer employment, which is used as a technique or methodology of training people that are the future scientists during the period that they go to school. But then you have the fourth problem that we discussed the other day; we have to count as year-end employment all of the consultants that are employed at any time during the month of June, and the fact that we have councils meeting in June gives us a large number of scientists that were there for only 1 or 2 days during the month but count as employees on the last day of the month.

RECRUITMENT OF COLLEGE GRADUATES

Mr. LESINSKI. Do you know Dr. Louis Levine, Director of USES?

Dr. SHANNON. No, sir; I do not know him.

Mr. LESINSKI. The subject was brought up of placements of college graduates in the U.S. Government, and I have read a pertinent letter here from the University of Detroit. I will read to you a few paragraphs that require explanation.

Dr. Louis Levine, Director of U.S. Employment Service, at a recent meeting of the Midwest College Employment Association, stated that his agency plans to take over the placement activity of college graduates whenever and wherever possible. He felt that the USES could do a much better job than colleges are doing, and that he had personnel and the money, resources, to do so.

This appears to be a gross attempt at empire building on the part of Dr. Levine in the activity where he is neither wanted, needed, nor qualified.

The subject was brought up here about recruiting of Federal employees, and I am just wondering whether the Labor Department is going a little too far.

Dr. SHANNON. Sir, this in no way interferes with, adds to, or subtracts from our own individual activities in recruitment on an individual basis within the general guidelines of the Civil Service Commission.

All I can say is Mr. Levine has neither interfered with nor helped us.

Mr. LESINSKI. Neither one of the two?

Dr. SHANNON. No, sir.

Mr. LESINSKI. Thank you.

I have no further questions.

HIGHLIGHTS OF PROGRESS IN RESEARCH IN GENERAL MEDICAL SCIENCES, 1962

ITEMS OF INTEREST ON PROGRAM DEVELOPMENTS AND RESEARCH STUDIES CONDUCTED AND SUPPORTED BY THE DIVISION OF GENERAL MEDICAL SCIENCES

ENDOCRINOLOGY

GROWTH-CONTROL SUBSTANCES FOUND IN THYMUS GLAND

The thymus gland at the base of the neck is largest in childhood and grows smaller with sexual maturity. Its functions are just beginning to be understood. In the course of the past year, two specially illuminating thymus studies have been reported.

The first is the fruit of many years of work at the Institute for Muscle Research, at Woods Hole, Mass., under the direction of Albert Szent-Györgyi, a Nobel prize winner whose studies have received support from the National Institutes of Health since 1948. His team has partially isolated from calf thymus two growth-control substances called promine and retine. The chemical composition of these substances is not yet known, but promine apparently promotes growth of the individual and retine retards it. The investigators believe the balance between the two is what determines normal growth and imbalance may well affect malignancy.

The two substances were tested on fast-growing cancers in inbred mice of the same age. There is no evidence that promine causes cancer, but it does accelerate cancer growth in all ages. The effect is more marked in old animals than in young ones. When retine was injected, the ascites tumors stopped growing after the second injection.

In addition, the investigators noted that promine made the mice temporarily sterile, and that it took twice as much to make females sterile as males. This observation fits in with the fact that the thymus is the largest in sexually immature young animals and regresses at puberty.

Evidence has been obtained lately indicating that the growth-promoting effect and the sterilizing effect are due to two different substances. There is a possibility that the thymus is also involved in myasthenia, a disease of muscle weakness.

This work by Szent-Györgyi, Hegyeli, and McLaughlin was published in the Proceedings of the National Academy of Sciences (48: 1439-1442).

THYMECTOMY REDUCES ANTIVIRAL DEFENSES IN NEWBORN MICE

At the University of Minnesota, a second thymus study has been guided by Dr. Benjamin Papermaster (under a medical student research training grant from this Division) and by Dr. Robert Good (under a National Heart Institute research grant). They report that inbred mice which had their thymus glands completely removed within 24 hours of birth were unable to make antibodies against a bacterial virus (*T₂* bacteriophage) injected into them 2 months later, while other mice of the same age and strain easily neutralized the virus with antibodies developed in their blood. Small fragments of the gland left by accident could grow rapidly enough to change the immunological reactions back toward normal. This research shows clearly that the thymus gland has a most important role in the defenses of the body against foreign substances.

The article by Papermaster, Dalmasso, Martinez, and Good was published in the Proceedings of the Society for Experimental Biology and Medicine (111: 41-43).

A SYNTHETIC MOLECULE HAS MANY PROPERTIES OF NATURAL HORMONE

Since 1951, the National Institutes of Health has supported the research of Dr. Choh Hao Li of the University of California, in Berkeley, where Dr. Li heads the Laboratory of Endocrine Research.

Dr. Li has isolated and identified six of the hormones of the anterior pituitary gland, and has divided them into fractions which influence growth, reproduction, milk supply, and various endocrine glands. He has established that human growth hormone has a different chemical structure from animal growth hormone, and that it is associated with milk production after childbirth.

In his biochemical studies, Dr. Li has established that 39 amino acids comprise ACTH, adrenocorticotrophic hormone of the pituitary, which stimulates the adrenal gland to manufacture cortisone. Recently he has been synthesizing similar but smaller molecules which function in the body with much of the effect of the whole molecule. This work encourages the hope of designing chemicals to promote one process separate from others. For example, a new synthetic hormone might stimulate growth without upsetting reproduction.

This year Dr. Li reported in the Journal of the American Chemical Society (84: 2460-2462) the production of a short molecule (17 amino acids) which has much of the ACTH activity and an even greater ability than the whole hormone to break down fats.

In recognition of the value of this basic research to medicine, Dr. Li has this year been given the Lasker Award.

PINEAL BODY IN RODENTS REDUCED IN SIZE AND LIPID CONTENT BY LIGHT

The pineal body is a light-sensitive part of the brain in some cold-blooded animals. In some mammals, including man, it appears microscopically to resemble an endocrine gland. Its function is still uncertain. Perhaps, like the appendix, it is vestigial in some higher animals. Recent work suggests that the pineal body is an endocrine gland containing in its secretory cells special indole amine and lipid-like compounds. The lipoidal material has been associated with the regulation of the adrenal hormone, aldosterone.

Working with inbred hamsters and rats, Wilbur B. Quay of the University of California in Berkeley is trying to learn more about pineal functions. He has found that continuous light for 4 weeks reduces the weight of the pineal body and the amount of lipid in it as compared with the effects of 14 hours of

light a day on similar animals. Adding sodium and potassium salts to the drinking water and removing both adrenal glands did not change this pineal response to light, but cutting across both optic tracts did block the response.

The investigator suggests that continuous light acts through the eyes as a chronic stress on the pineal body. More study is needed to learn whether the loss of lipids from the pineal body is due to an increased rate of lipid secretion or a decreased rate of lipid accumulation. Also unknown is why animals reared in darkness, or at high temperatures with only 15 minutes light a day, or females in heat, did not show the usual pineal reactions to continuous light.

This search for relationships between a part of the brain and the chemistry of the body was reported in *General and Comparative Endocrinology* (1: 211-217).

INACTIVE-TYPE INSULIN MAY CAUSE DIABETES AS WELL AS LACK OF HORMONE

Diabetes has long been studied, but it is only recently that more than one condition has been shown to produce the same "diabetic" symptoms. In all diabetes there is defective insulin activity, but this is not always because too little insulin is made.

H. N. Antoniades and H. M. Pyle of the Protein Foundation, Inc., and J. A. Bougas of the Overholt Thoracic Clinic, in Massachusetts, have reported that in some cases the pancreas secretes active free insulin normally, but when that insulin circulates in the blood, it is chemically bound into a complex inactive form. The mechanisms for this binding and release of insulin are not yet completely understood. Apparently, the liver is one place where the binding occurs and extracts from fatty tissues seem to contain the factors which release the complex bound insulin.

Diabetic and nondiabetic people were both given sugar, then samples of blood were taken simultaneously from arm veins (after the blood had been through the liver) and from the portal vein (after the blood left the pancreas but before it reached the liver). In both groups, the blood from the portal vein had free insulin. Blood from arm veins of nondiabetic people had a mixture of free and bound insulin at first, but after 10-20 minutes only free insulin. After an hour, arm blood in diabetics still contained mostly bound insulin despite the rise in blood sugar.

The investigators also point out that if the normal insulin-binding process should fail, the result could be a pathological reduction of blood sugar—just the opposite of pathological excess of blood sugar, which is diabetes.

This research was published in the *New England Journal of Medicine* (267: 218-222).

CELL BIOLOGY

CELLULAR ENERGY CHANGES IN ANIMALS CORRELATED WITH SUPPLY OF OXYGEN

Investigators at the University of Pennsylvania have detected and recorded energy changes produced within brain and kidney cells by varying the animal's supply of oxygen.

The energy animals derive from food is utilized by changes in various phosphate compounds (pyridine nucleotides). Some electrons in these molecules shift or "flow" in cycles as energy is alternately stored or yielded. Since these phosphate compounds show intense fluorescence at characteristic wave lengths when stimulated by ultraviolet light, energy shifts can be monitored by machines (fluorescence spectrometers).

Dr. Britton Chance has been able to note cellular energy changes in living animals for hours at a time because as energy is spent the fluorescence increases.

Dr. Chance found that nitrogen, cyanide, and carbon monoxide gases cause practically the same amount of energy loss in rats. In low blood concentrations, the sedative, Amytal, leads to energy loss in the kidney, and at high concentrations, to energy loss in the brain. The brain appeared to be 10 times more sensitive to oxygen deprivation than the kidney. When the oxygen supply was reduced to 8 percent, the brain began to show energy loss and when 90 percent of the phosphate compounds in the brain had lost electrons the rat stopped breathing. At this stage, however, only about 30 percent of the kidney phosphate compounds had lost electrons.

According to Dr. Chance, living animals, tissue slices, and mitochondria extracted from cells show similar fluorescence changes when their supply of oxygen fails. Because these fluorescence changes correspond with the gain or loss of

electrons, of the phosphate molecule, the use of spectrofluorometer techniques should enable investigators to measure oxygen concentrations in various parts of living animals. Dr. Chance also suggests this method for studying the effects of drugs on energy changes, and for comparing the reactions of homogenized and extracted parts of organs with reactions in living organs.

This research was described by Chance, Cohen, Jobsis and Schoener in *Science* (137: 499-508).

HYDROGEN SUBSTITUTED FOR SUNLIGHT TO POWER PLANT ENERGY CHANGES

In recent years scientists have learned that plants use light energy first to combine phosphorus and hydrogen into high energy compounds called ATP (adenosine triphosphate) and TPNH (reduced triphosphopyridine nucleotide), in a process called photosynthetic phosphorylation. This is important because ATP and TPNH are found in every plant, animal, and microbe wherever chemical energy is used in the business of living. These phosphorus compounds are essential in the making of sugars and starches.

Daniel Arnon and his associates of the University of California in Berkeley discovered photosynthetic phosphorylation in isolated chloroplasts, the small bodies in which higher plants store the green pigment chlorophyll. Other tissues make ATP by respiration but chloroplasts do not respire. Respiration is that part of metabolism which carries on oxidation (burns up chemical energy) in tissues. Previous to Arnon's discovery, it was hard to study ATP formation in photosynthesis because it could not be separated from ATP formation in respiration, since both took place at the same time in the same cell. By removing the chloroplasts from the cell, it was possible to study the way the green pigment reacted with light without having to take into account the normal physiology of the rest of the cell.

Arnon developed an electron-flow theory to explain how, in plants, the chlorophyll molecule captures a small amount (quantum) of light energy and transfers it so that eventually phosphorus may be fashioned into its high-energy compounds. Once solar energy is transferred into chemical energy, metabolism can release it when and where it is needed in an organism.

This year Kunio Tagawa and Arnon reported in *Nature* that they had substituted the chemical energy of hydrogen gas for the energy of sunlight, and found that, in the dark, isolated spinach chloroplasts could use this chemical energy to make TPNH. The investigators believe that this most recent work adds strong support to their electron-flow theory. An outside source of energy (light or hydrogen) strikes a chlorophyll molecule or an enzyme and pushes one of its electrons into an "excited state" or a higher energy level. This electron is then so loosely attached to the parent molecule that it can easily be captured by some other nearby molecule which is short of an electron.

The energetic electron may be passed from molecule to molecule, gradually losing energy as it goes. In this case the transferring molecule was an iron compound called ferredoxin, recently identified by other scientists in bacteria, and found also in spinach by Arnon's team. See *Nature* (195: 537-543).

SPECIAL PARTS OF DIVIDING CELLS SEPARATED FROM REST OF CONTENTS FOR ANALYSIS

For years biologists have tried to discover the forces and processes involved in cell division, because this activity, called mitosis, determines how plants and animals apportion to their descendants the chemical blueprints of their lineage, and explains their differentiation, growth and repair processes. In most cells during cell division special structures may be seen (asters, spindles, and chromosomes) which are called collectively the mitotic apparatus. Scientists thought that if they could separate this apparatus from the rest of the cell contents in sufficient quantity, they might make chemical analyses of factors in cell division.

A decade ago, Mazia and Dan, using alcohol and a detergent, succeeded in proving the existence of this apparatus by isolating it from the cell. They then discovered, by chemical analysis, that their method had damaged the chemical, though not the physical, structure of the apparatus, because such universal chemical properties of cells as the ATPase enzyme were missing.

Recently, Mazia's group, working at the University of California, in Berkeley, has developed a new method using sucrose, dithiodiglycol, and versine. In this procedure the cell membrane can be broken and the cell contents dispersed, leaving the mitotic apparatus intact and looking as it does in the living cell. The investigators realize that the new method may introduce new errors, but ex-

plain, in terms of chemical bonds (particularly of sulphur), the rationale of their methods, and the reasons why they expect the chemical analyses resulting from the new technique to complement the previous work and to expand information about various forces which affect the stability of the apparatus, enzyme activities, and lipid components involved in cell division. Since cell biology is the chief key to the understanding of genetic defects, virus diseases, cancer, and some mental diseases, each ray of light on the mechanism and chemistry of cell division is important.

Daniel Mazia, J. M. Mitchison, Heitor Medina, and Patricia Harris contributed to this work, which was reported in the *Journal of Biophysical and Biochemical Cytology* (10: 467-474).

RADIOLABELING SHOWS RNA SYNTHESIZED ON CHROMATIN FIRST IN ISOLATED NUCLEI

Ribonucleic acid (RNA) is the substance in cells which controls the manufacture of proteins. Since understanding the reactions of RNA and the other nucleic acid, DNA, is expected to provide keys unlocking secrets of heredity and growth, much of today's basic research is on this subject.

James Bonner of the California Institute of Technology in Pasadena heads a laboratory active in this area. One of the studies by J. H. Rho and James Bonner used a new method of separating nuclei from the cells in the embryos of pea seeds. The isolated nuclei were allowed to react with tritium-labeled cytidine, a precursor of RNA. After various time exposures the reaction was stopped by chilling. The solution was then replaced with nonradioactive ingredients, and the nuclei were finally broken up and separated into fractions consisting of chromatin, nucleoli, and ribosomes. Each fraction was examined for RNA production.

The scientists noted that cytidine is rapidly incorporated into RNA in the chromatin, but in the nucleolus only after a long time lag. They concluded that the RNA itself is synthesized first on the chromatin and later transferred to the nucleolus.

This work was reported in the Proceedings of the National Academy of Science (47: 1611-1619).

BACTERIAL RNA MAKES CHICK CELLS PRODUCE BACTERIAL PROTEIN IN TISSUE CULTURE

Watching the ways living cells react to changes in the solutions in which they are grown outside of the body has been a very fruitful method of study, useful for learning the effects of drugs and the requirements of various tissues. It has also served as a tool for more basic studies.

When connective tissue cells (fibroblasts) are isolated from chick embryos and grown in thin layers on glass, researchers have noticed a one- to two-day delay before the cells resume normal protein production. This delay can be shortened by adding ribonucleic acid (RNA) to the culture medium. Chick cells use RNA from other chicks, from rabbit liver, or from the bacterium *Escherichia coli* equally. Only when RNA has been broken down by pretreatment with the enzyme, ribonuclease, is protein manufacture not increased.

A form of RNA, called messenger RNA, apparently has the task of directing the assembly of amino acids according to preset patterns to make specific proteins characteristic of a specific animal or plant.

Harold Amos and Katherine E. Kearns, of Harvard University, thought it might be possible for chick cells to make some bacterial proteins under the direction of the foreign bacterial RNA in the culture medium.

Although they did not find bacterial enzymes in the cultured chick cells, they did find that 5 to 15 percent of the total protein made in the chick cells after exposure to bacterial RNA were bacterial antigens. Similar chick cells, grown in a medium without bacterial RNA, made no bacterial antigens.

This ability of foreign RNA to penetrate intact cells and to direct the synthesis of some proteins resembles the action of viruses, and strengthens the theory that there may be a universal RNA code for all living creatures.

This work was reported in *Nature* (195: 806-808).

STRUCTURE AND FUNCTION STUDIED IN FISH MUSCLE SARCOPLASMIC RETICULUM

Scientists interested in muscles would like to know more about the contraction process, and with the help of the electron microscope they are making progress in seeing relationships between muscle structure and function.

D. W. Fawcett and J. P. Revel of the Harvard Medical School selected for study a striated muscle in the wall of the toadfish's swim bladder. This muscle produces the characteristic sound of the toadfish by alternately contracting and relaxing so quickly that it produces audible vibrations in the swim bladder. Because this is more rapid contraction than most vertebrate muscles can manage, the investigators tried to account for the speed of contraction and to discover what structures might make possible such an expenditure of energy in a muscle cell.

The electron microscope has shown that in many cells the cytoplasm contains a network of tubes called the sarcoplasmic reticulum and packages of enzymes called mitochondria arranged to produce energy as needed. Muscle fiber cells have, in addition, special contractile elements rather like coiled springs called myofibrils.

In the toadfish, Fawcett and Revel found the tubular sarcoplasmic reticulum more elaborate and its relations with the muscle fibers easier to analyze than in most muscles. The more elaborate structure in this instance would support the prevailing concept that the tubular structure of the sarcoplasmic reticulum serves to conduct impulses from the surface of the cell inward to activate the contractile myofibrils which lie in the interior of the muscle fibers.

These investigators, however, propose another possible function based on their observations of form. Since the mitochondria in the sarcoplasm of this muscle are found only in the central core or pressed against the outer surface membrane of the muscle fibers, and since the distance between these energy packets and some of the contractile fibrils is considerable, it is possible that the reticulum may serve to distribute with speed and uniformity to all parts of the muscle fiber, where energy is needed to power contraction, the compounds produced in the mitochondria.

This article appeared in the *Journal of Biophysical and Biochemical Cytology* (10 (pt. 2) : 89-110).

MICROBIOLOGY

STUDY MADE OF CAUSATIVE FUNGI AND THERAPY MINUS STEROIDS IN EYE ULCERS

Physicians usually treat eye ulcers, especially those following damage from some foreign object, with ordinary antibiotics. If the infections do not clear up promptly, steroids are given to reduce inflammation and to make patients more comfortable.

Many stubborn infections resist this therapy, as Wendal D. Gingrich of the University of Texas, in Galveston, points out, because they are caused not by bacteria but by fungi. Moreover, many of these fungi have always been considered nonparasitic and harmless, so that even when identified, physicians have not always recognized their disease potential. Also, conventional pathological laboratories may not detect fungi because these organisms require culture methods different from those of bacteria. Nevertheless, discovery and identification of the troublemaking organism are essential for correct treatment.

Dr. Gingrich has found that use of adrenocortical steroids is often associated with relapse in the treatment of fungal eye ulcers, and that even fungicides when used only every 4 hours may not be adequate for stubborn infections. His experience shows that thimerosal or sulfacetamide solutions applied every hour will usually clear the surface infections, and that iontophoresis (an electrical treatment causing ions of the drug to penetrate undisturbed tissues) with sulfacetamide clears the deep infections.

This work was reported in the *Journal of the American Medical Association* (179 : 602-608).

EXPERIMENTAL STUDY MADE OF THERAPY AND REACTIONS IN FUNGAL SKIN DISEASE

Healthy people are highly resistant to moniliasis of the skin, a disease caused by the yeastlike fungus, *Candida*. Howard Maibach and Albert Kligman of the University of Pennsylvania, in Philadelphia, have found a way to induce *Candida* infections at will on healthy skin. To produce the disease it is necessary to apply more than 100,000 organisms in one spot and to seal that area so tightly that no drying can occur. Of the *Candida* species tested, only *albicans*, *stellatoidea* and *parakrusei*, in descending order of virulence, caused experimental infections.

Once a method for producing experimental infections was found, it was possible to study various aspects of moniliasis and the effects of drugs on the disease.

The investigators were able to induce moniliasis with equal ease and severity at any season, in various races, and over most areas of the skin. The palms of the hands, the soles of the feet and the scalp appeared to be invulnerable. Efforts to produce lesions in the mouth (thrush) were also unsuccessful. *Candida* was not found within living epidermis but was restricted to the outer layers of the stratum corneum and disappeared rapidly after inflammation developed.

Bacterial antibiotics and corticosteroids neither aggravated nor alleviated these experimental infections. The investigators were not able to induce secondary infections by applying the fungus to skin previously irritated by psoriasis, by freezing, or by ultraviolet burns. Gentian violet and nystatin, commonly used to treat *Candida* infections, prevented the experimental disease only when applied at the same time as the organisms. When the drugs were applied 24 hours later, the disease occurred as usual.

Maibach and Kligman report that they found little evidence of allergy to *Candida* even in people repeatedly infected with this organism. They also report that a sterile extract of the fungus produced the same inflamed skin condition as did living cells. Hence, they conclude that this elusive fungus releases a potent endotoxin-type irritant on the surface of the skin.

This work was reported in the Archives of Dermatology (85: 233-257).

MODERN ANTIVENIN WITHOUT CLOSTRIDIAL ANTITOXINS PROTECTS IN SNAKE BITES

Antivenin used to treat snakebite prior to 1954 was unsatisfactory, since about 25 percent of eastern daimondback rattlesnake bites so treated proved fatal. Because the flesh around rattler bites was usually severely damaged, many authorities believed bacteria, which grow where air is excluded, must be present. They therefore advised using tetanus and gas gangrene antitoxins in addition to antivenin when treating snakebites.

Frank J. Fischer, Howard W. Ramsey, Joseph Simon, and Joseph F. Gennaro, Jr., of the University of Florida, at Gainesville, have evaluated modern antivenin (Wyeth). Their tests showed that no bacteria which grow in the absence of air and few which grow in the presence of air are found in the mouths of recently captured snakes. Only snakes kept long in captivity and frequently milked for venom were likely to harbor these organisms.

Tests indicated that 23 of 25 mice protected with the new antivenin survived over 72 hours and showed little skin damage, whereas all unprotected mice died within 2½ hours from the same dose. Moreover, the bacterial antitoxins neither prevented death nor improved the condition of the skin around the injection area. A further test on rabbits indicated that skin, after protection with the new antivenin, showed little damage compared with that produced by venom before the animal was protected.

For these reasons Gennaro and his coworkers feel that the use of tetanus and gas gangrene antitoxins (unless laboratory tests show such organisms to be present) is unnecessary, and that the modern antivenin is adequate protection.

This study appeared in the American Journal of Tropical Medicine and Hygiene (10: 75-79).

PHYSIOLOGY

CHILDREN REARED AT HIGH ALTITUDES HAVE HEARTS LARGER ON RIGHT SIDE

Adaptations enabling people to live where there is little oxygen and a reduced barometric pressure are of interest not only to mountain climbers and space explorers, but for the understanding of the range, possibilities, and mechanisms of human endurance. When for centuries large numbers of people have lived at high altitudes, their adaptations can be most significant. In Lima, Peru, these conditions have provided the setting for a number of high altitude studies.

Javier Arias-Stella and Sixto Recavarren of the faculty of medicine of Lima, have reported a study of the hearts of children born at high altitudes compared with those born at sea level.

Babies at birth usually have a right ventricle equal to, or larger than, the left, but by the age of 3 months the left usually predominates. Older people who move from sea level to high altitudes maintain the larger left ventricle. Their way of adapting to the smaller supply of oxygen is to make more red blood cells.

The Lima investigators report a study of the hearts of 129 Peruvian children who had died from accidents or acute illnesses and who showed no changes in their circulatory systems from disease. Seventy of these were born at sea level and 59 were born at altitudes over 10,000 feet. The children ranged from newborn to 10 years of age. The hearts were carefully dissected and each half weighed. Most hearts from the high-altitude children retained the larger right ventricle characteristic of the newborn. The investigators suggest that this condition indicates a higher blood pressure in the pulmonary arteries and may be an adaptation useful for living in a low oxygen environment.

The work was published in the *American Journal of Pathology* (41: 55-65).

CERVICAL MUCUS PROTEINS VARY PERIODICALLY AND HAVE ANTIBODIES TO BLOOD GROUPS

There are thousands of couples who are unable to have children although they are to all appearances perfectly normal and healthy. At Wayne State University in Detroit some of the answers to such sterility are being sought in analysis of the chemistry of cervical mucus, particularly the proteins, in both fertile and sterile women.

By using a combination of electrophoretic and immunological techniques, they have found albumin, gamma globulin, five of the beta globulins, and three of the alpha₂ globulins, in this order, and in decreasing amounts in normal mucus. The relative proportions of these proteins vary with the menstrual cycle, decreasing in the midcycle phase.

Based on previous work using injections of radioactive proteins into the blood stream, Kamran S. Moghissi and Otto W. Neuhaus deduce that cervical proteins probably come from blood serum proteins, but not merely by filtering through vessel walls.

The mucous proteins include those containing the blood antibodies and also antibodies against the ABO blood-group antigens. These proteins, because of their possible antibody-antigen relationships to sperm, are important in the study of unexplained human infertility. The authors suggest the possibility that the germ cells of one partner are allergic to the environment of the other.

This research was reported in the *American Journal of Obstetrics and Gynecology* (83: 149-155).

CHEMICAL STUDIES SUGGEST SKIN MUCOIDS IN PSORIASIS CEMENT CELLS TOO LONG

Molecules of simple carbohydrates, such as sugars, are sometimes fastened together making complicated polysaccharides. Polysaccharides are sometimes combined with proteins, resulting in mucopolysaccharides. For years, the best known example of a mucopolysaccharide was chitin, the principal ingredient in the outside covering of insects. Until the last decade the only comparable material in animals higher than fish was thought to be keratin, which belongs to a different chemical family. Keratin is the basis of horn, tooth, enamel, and hair.

In recent years accumulated evidence has indicated that mucopolysaccharides are present even in man, and that cells deep in the skin can make either the mucoids, or keratin, or both, in balance. Upon the balance depends the surface conditions of skin, hair, nails, and so forth.

Daphne Roe, Peter Flesch, and Elizabeth C. J. Esoda of the University of Pennsylvania, Philadelphia, believe that normally mucoids serve as cements to hold epidermal cells together. They reason that the mucoids gradually decompose as keratin is formed in healthy human skin. This decomposition enables the skin to shed the horny outer cells continuously in minute flakes.

In certain skin diseases, especially psoriasis, the authors consider that the metabolism of the mucoids changes. The cementing action persists and keratin-filled cells are held together until large flakes are formed.

Psoriasis, a scaly, stubborn skin disease affecting an estimated 2 million people in this country, has been studied clinically and biochemically by these investigators. They decided to try substances known to affect mucopolysaccharide metabolism, and have reported that aromatic basic diamidines greatly improved the condition of patients under study. At the time the study was published, it was not known whether the drug interfered with formation of the keratin or with formation of the mucoids. However, later investigation established that it was the formation of the mucoids that was affected.

The theory and evidence are presented in *Archives of Dermatology* (84: 213-218).

MAGNESIUM IONS AFFECT MUSCLE SWELLING MORE IN OLD THAN IN YOUNG PEOPLE

As part of a study on the biology of aging, R. R. Kohn, H. Keye, and E. Roller-son, of Western Reserve University, Cleveland, Ohio, tested reactions of skeletal and smooth muscle to solutions of sodium, potassium, and magnesium salts. Muscles from people of various ages, from 5 months to 84 years, were used. The effects of the various chemicals, the degree of alkalinity of the solutions, and the amount of swelling in both types of muscle were compared.

Apparently the removal of magnesium increased muscle swelling in alkaline solutions, whereas its addition inhibited swelling. Old muscles contained more magnesium than young. However, old muscles lost more magnesium than young in solutions of the same concentration and consequently swelled more. Whether these reactions are due to differences in cell permeability or to magnesium binding is not clear, but the study may help to account for muscle weakness in old age.

These data were published in *Experimental Cell Research* (25: 170-175).

CARTILAGE CELLS MAY RESPOND TO PRESSURE BY ACTIVE DIVISION

Cartilage is important in the joints, ears, and nose. It is durable, but when damaged it is repaired very slowly or not at all. In the mature state cartilage cells (chondrocytes) are generally supposed to be unable to divide. The breakdown of cartilage following continuous pressure on joints is usually considered to be due to interference with the diffusion of nutrients through its matrix and hence with the nutrition of the cells.

However, W. O. Southwick and E. S. Crelin, of Yale University, subjected rabbit knees to pressure for 16 days. At the end of that period they were able to demonstrate microscopically some actively dividing cartilage cells. These cells appeared not only in the area damaged by pressure, but also in the intact cartilage at the edge of the damage, demonstrating that cartilage cells may react to injury produced by pressure by undergoing mitotic division.

This work was reported in *Surgical Forum* (12: 443).

OXYGEN SECRETED UNDER TENSION IN EYES OF ACTIVE PREDACEOUS FISH

Oxygen is essential for combustion in the body furnace, and it is necessary to understand the numerous ways living creatures provide oxygen to their various parts. Physiologists trying to determine the source of oxygen necessary to supply the energy requirements of the retina in the eye have been puzzled by the lack of blood vessels, the usual oxygen carriers, in the chorion.

Jonathan B. Wittenberg and Beatrice A. Wittenberg, of Yeshiva University, in New York City, observed that some fish have associated with their retinas an organ called a rete mirabile, in which the smallest arteries and veins are arranged in network layers. This type of organ is also associated with swim bladders of fish. Over 150 years ago Biot found that fish captured at great depths had swim bladders filled with pure oxygen apparently secreted into these bladders at partial pressures up to 85 atmospheres. Since that time, physiologists have searched in vain for other examples of oxygen secretion.

Consequently, when the Wittenbergs observed the rete organ close to the eyes in some fish, they investigated whether unusual oxygen tensions might also be present there. They studied oxygen secretion in 18 varieties of fish with widely differing habits by placing a special oxygen-measuring electrode just in front of the retina. Fish without a rete mirabile had very little oxygen in that area. In species in which that organ was small, and the fish lived on the bottom eating what could be sensed chemically, there was a modest amount of oxygen. Strong oxygen pressures occurred (for example, in the remora) when the rete was well developed. In these cases, fish are predaceous and apparently depend upon keen vision to recognize, follow, and catch their food.

In both the swim bladder and the eyes of these rete-bearing fish the oxygen is transported against a large concentration difference, but whether most cells can transport oxygen, and the rete mirabile acts only as a countercurrent multiplier to collect a supply in one place, or whether the rete and retina work together as a special oxygen transporter, is not yet known.

This work was reported in *Nature* (194: 106-107).

BABY JAUNDICE DIVIDED IN FOUR TYPES, WORST OF WHICH HAS FREE SERUM BILIRUBIN

W. W. Zuelzer, L. E. Reisman, and A. K. Brown, of the Child Research Center of Michigan, in Detroit, have investigated jaundice in 50 premature infants to learn why some with high bilirubin levels show few other signs of illness, and recover, while others require exchange blood transfusions to survive. It was not until Eberlein developed a sensitive solvent partition method of chromatography in 1960 that it became possible to study this problem in infants by measuring in blood serum the amounts of free bilirubin and its two conjugated forms, bilirubin diglucuronide and bilirubin monoglucuronide.

None of the infants selected for the Michigan study had Rh or ABO blood group incompatibilities, and all were divided into groups according to size. The smaller babies, and those with respiratory difficulties, generally showed more jaundice.

The investigators distinguished four patterns of jaundice based on the relative distribution of bilirubin and its derivatives. Apparently free bilirubin is converted first to the monoglucuronide and then to the diglucuronide form to facilitate excretion. Severe illness was associated with accumulation of free bilirubin. High concentrations of the monoglucuronide are usually self-limiting, as the liver soon matures enough to handle the pigment load.

Jaundiced babies who have respiratory difficulties tend to have high serum concentrations of free bilirubin. The investigators note that normal carbohydrate (glucose) metabolism depends upon a good supply of oxygen, and suggest that the inability of these infants to combine bilirubin with the monoglucuronide is part of this general metabolic problem and may mask the further inability of the immature liver to form the diglucuronide compound and to excrete the pigment.

These studies were reported in the *American Journal of Diseases of Children* (102: 815-842).

PROLINE FOUND IN BLOOD AND URINE OF FAMILY WITH OTHER HEREDITARY DEFECTS

Recent investigation of several severe congenital handicaps in a single family has shown the presence of a metabolic defect called hyperprolinemia, associated with kidney defects, deafness, and a form of epilepsy.

The blood and urine of both the parents and six children were studied. The chief sufferer, a boy, and three of his sisters had an unusually high concentration of proline in their blood serum, although the other amino acids were present in normal amounts. In three of these four children the urine showed excess glycine, hydroxyproline, and proline. Normally proline disappears from urine after the first few months of life.

C. R. Scriver, of the Montreal Children's Hospital, Canada, and I. A. Schafer and M. L. Efron, of the Children's Medical Center in Boston, who studied the family, concluded that proline, hydroxyproline, and probably glycine are transported in the same way by the kidney tubules.

The relation between the excess proline and the other disabilities in this family is still under genetic and chemical study. Intermittent bloody urine (hematuria) and small undeveloped kidneys are present along with nerve deafness and epileptic attacks triggered by flickering light.

In 1961, M. M. Cohen, G. Cassady, and B. L. Hanna, of the National Institute of Dental Research, reported a study of 22 families in which nerve deafness occurred, along with intermittent hematuria. They interpreted their evidence as showing that this condition was due to a dominant gene in one of the chromosomes (an autosome, not a sex chromosome). This gene appears to move in association with the X chromosome rather than at random when the chromosomes are separated (meiosis) prior to forming eggs and sperm.

As far back as 1902, families with intermittent hematuria were reported. Among the earliest cases there was one with epilepsy, but no mention was made of other problems such as deafness.

It is by collecting and recording observations over many years (60 in this unfinished example) that these genetic puzzles begin to make a picture. Investigations of families with rare metabolic defects are helping us to understand the mechanics of transfer of genetic information.

The hyperprolinemia study was reported in *Nature* (192: 672-673).

PENICILLIN DAMAGE TO CELL MEMBRANE LOWERS BACTERIAL RESISTANCE TO STREPTOMYCIN

Scientists have observed that destruction of various bacteria, both in test tubes and in some human infections, may be more effective when both penicillin and streptomycin are used than when either is used alone. The mechanism of this effect has been studied by Paul H. Plotz and Bernard D. Davis, of Harvard University.

When several strains of *Escherichia coli* organisms were exposed briefly to streptomycin before treatment with penicillin, the killing power of the penicillin was not increased. However, when the bacteria were first treated briefly with penicillin, far less streptomycin was required to kill the organisms than when streptomycin was used alone. Even organisms exposed to penicillin, then removed and allowed to multiply in a normal growth medium, were more easily killed by a subsequent dose of streptomycin.

Studies of the uptake of radiolabeled substances suggest that both drugs damage the cell membrane but that the damage by penicillin, which is indirect, facilitates penetration of streptomycin into the cell. A streptomycin-resistant strain of bacteria was not made less so by pretreatment with penicillin. This protective mechanism is being studied.

This research was reported in *Science* (135: 1067-1068).

DISTURBANCE OF MEMBRANE CHEMISTRY FOUND PRIMARY DAMAGE TO RED BLOOD CELLS

Harry S. Jacob and James H. Jandl are working at Harvard toward an understanding of the reasons why red blood cells break down in disease or under laboratory conditions. They are seeking the why, where, and when of this kind of red cell destruction to find answers to some problems of anemia.

One part of their work, which appeared in the *Journal of Clinical Investigation* (41: 779-792), was a study of the effects of two chemicals on the red blood cell. Previously, several investigators had shown that in red blood cells the amount of glutathione (a sulfhydryl compound) drops in certain hemolytic anemias, also that a number of substances can reduce sulfhydryl activity in cells. But the question remained whether sulfhydryl activity was disturbed by chemicals reacting within the cell or at the cell membranes.

Jacob and Jandl experimented with N-ethylmaleimide and *p*-Mercuribenzoate, both of which inhibit sulfhydryl activity, but the former freely enters the cell, whereas the latter carries a positive electrical charge, and therefore cannot penetrate the cell membrane.

Within the red cells, N-ethylmaleimide blocked the production of glutathione, prevented the breakdown of sugars, and disturbed the normal relationships of positive ions so that potassium was lost and sodium gained. Water entered the cell, which then lost its disk shape, swelled to a sphere, and finally lost its hemoglobin and disintegrated.

The *p*-Mercuribenzoate, which could not enter the red cell and so could not change its internal glutathione and sugar relationships, nevertheless disturbed the flow of positive ions at the cell membrane, so that water was also absorbed, cellular swelling occurred and in time hemoglobin was lost.

From these test tube experiments Jacob and Jandl conclude that shape and viability in red blood cells depend primarily upon the activity of the sulfhydryl compounds of the cell membrane and not of those within the cell.

AFFINITY OF ANESTHETIC GASES FOR PROTEIN AND WHY INERT GAS REACTS STUDIED

Some years ago, R. M. Featherstone of the University of California noticed that he could detect and measure the entrance of radiolabeled xenon, an inert gas used as an anesthetic, into a dog's brain, but he was not able to determine its rate of exit. Only after the plastic polymer tube (used to conduct the blood through the radiation detection system) was replaced with glass, was he able to measure the rate of exit of the xenon. This clue led him to speculate that perhaps inert gases might have special affinity for biological polymers; namely, proteins, and perhaps this protein relation, rather than the previously studied lipid relation might explain why an inert gas, which usually takes part in no chemical reactions, nevertheless produces the profound reactions of anesthesia. Perhaps the gas-protein relationship might also account for some aftereffects of anesthesia.

Featherstone and his coworkers, C. A. Muehlbaeher, F. L. DeBon, and J. A. Forsaith at the University of California, San Francisco, have reported that in normal whole blood water amounts to 80 percent, lipid to 0.56 percent, and protein to 18 percent; but when the amounts of various anesthetic gases in solution in the water and lipid fractions of the blood were calculated, large percentages were still unaccounted for. Using purified human serum albumin in various concentrations for the protein and cyclopropane for the anesthetic gas, these investigators noted that more gas went into solution as more protein became available, and that when the albumin was 18 percent of their solution, nearly as much gas dissolved in their preparation as was found in whole blood.

Curiosity about the mechanisms whereby inert gases may modify the structure of protein molecules to produce anesthesia led the authors to several theoretical explanations. One assumes mechanical disruption of the protein molecule by penetration of the gas molecule. Another presupposes changes in the electrical charges (dipoles) at the outer edges of these large protein molecules. A third involves the possibility that there may be an increase in solubility of inert gases when organic solvents (such as chlorethanol) or changes in pH cause some proteins to assume a helical shape. The authors propose to follow these lines of investigation further. They reported their findings in *Anesthesiology* (22: 977-981).

ENZYME CHEMISTRY

MUSCLE DAMAGE IN RABBITS LACKING VITAMIN E WORSE AS SIX ENZYMES INCREASE

Muscular dystrophy is a little understood disease in spite of considerable research efforts in this country and abroad to clarify its cause and modify its course. Symptoms similar to those of human muscular dystrophy develop in rabbits kept on a diet deficient in vitamin E, and this allows an experimental study of the chemistry of tissue degeneration.

In many organs the cytoplasmic part of the cells contains lysosomes, which are minute storage units of enzymes. Lysosomal enzymes have a special relation to lipids or fats, and may be extracted by detergents. When vitamin E is present, oxygen does not combine with fats to form poisonous peroxides, lipid-protein membranes stay intact, and lysosomal enzymes remain bound in the lysosomes.

H. Zalkin, A. L. Tappel, K. A. Caldwell, S. Shibko, I. D. Desai, and T. A. Holliday, studying chemical changes in the absence of vitamin E, think peroxidation is a vital link in rabbit muscle degeneration. Peroxidation, when not prevented by vitamin E, seems to damage lipid-protein membranes and to release lysosomal enzymes. Then phagocytic cells, which are also rich in lysosomal enzymes, enter the damaged tissue as scavengers to clear away the debris. The result in injured muscle is a rise in the concentration of 6 lysosomal enzymes from 10 to 60 times the normal amount. The amount increases with the length of time the rabbit lives on its E-deficient diet. Moreover, the increase of five of these enzymes can be detected as soon as, or sooner than, the earliest previous urinary creatine test for muscular dystrophy. The investigators feel that lysosomal enzymes play a major part in the development of muscle damage through their destructive catabolic actions, and are not merely a side product of the process.

This research, done at the University of California, Davis, encourages hope that understanding the mechanisms of experimental muscle disease may in time lead to relieving other forms of muscle disease. The report appeared in the *Journal of Biological Chemistry* (237: 2678-2682).

STUDY ADVOCATED OF ANIMAL SERUM ENZYMES FOR USE IN NEUTRALIZATION OF POISONS

It has long been recognized that many animals have a natural tolerance to substances which are poisonous to man. H. Shirkey of the Children's Hospital of Birmingham, Ala., and G. C. Schmidt, R. G. Miller, L. Honkomp, and G. Flamm of the University of Cincinnati, Ohio, are exploring ways of using this tolerance to help people.

They follow the theory that certain enzymes found in the sera and tissues of these animals enable them to resist poisons for which people have no natural protection. For example, the enzyme atropinesterase is found in the sera of some strains of rabbits but not in others. This enzyme can break down atropine and a few other drugs and poisons. Rabbit serum containing atropinesterase can apparently inhibit the action of atropine in mice, as is shown by lack of response of the pupils of the eyes to doses of this drug.

These investigators found that anti-whooping cough serum prepared from some rabbits, presumably containing atropinesterase, was helpful in treating a few atropine-poisoned children (aged 1-5), although in these cases the atropinesterase content of the serum had not been studied.

Obviously, more work needs to be done on this subject before its potential for counteracting poisons can be realized. The specific chemical substances which produce tolerance to both plant and animal toxins must be traced, and their safety for human use determined. The investigators are continuing research in this field.

This kind of development in the field of enzyme chemistry is just a beginning. However, one can see that it would be much better to use a purified enzyme to break down or destroy a poison than to use complicated antidotes of uncertain action.

This work was reported in the *Journal of Pediatrics* (60: 711-716).

ENZYME TEST ENABLES DIAGNOSIS OF RARE METABOLIC DISEASE

The rare glycogen storage diseases are apparently hereditary metabolic defects due to recessive genes. This congenital condition causes enlargement of the organs which store glycogen. The disease frequently results in dwarfism in children, associated with obesity, acidosis, and increased susceptibility to infections.

In type III glycogen storage disease the characteristic liver enlargement and lowered blood sugar is caused by the absence of one enzyme, amyl-1, 6-glucosidase. Glycogen ordinarily is changed in the liver by the combined action of the enzymes, phosphorylase and amyl-1, 6-glucosidase, to provide blood sugar. When glucosidase is missing, phosphorylase is able to break down only the outer chains of the glycogen molecule leaving a substance related to dextrin, which the body cannot use and which is stored in the liver in increasing amounts.

Barbara Illingworth and David H. Brown of Washington University, St. Louis, Mo., have derived a particular oligosaccharide (Fast B₅) from rabbit muscle glycogen. This substance is specific for the glucosidase. By studying the reaction of Fast B₅ with a small amount of tissue taken during liver biopsy, the investigators can determine when the enzyme is missing, and make the diagnosis of this particular type of glycogen storage disease.

The methods and results, tested in a series of 12 cases, were reported in the *Proceedings of the National Academy of Sciences* (48: 1619-1623).

EXCESS ENZYME CHECKS PRODUCTION OF MORE ENZYME BY RESHAPING MOLECULE

Catalysts are substances which speed up chemical reactions, but are not consumed in the process. In living creatures the catalysts are proteins with complicated molecular structure called enzymes.

Two shorthand phrases used by biochemists to describe one of the ways enzymes work are feedback inhibition and enzyme repression, a process analogous to thermostatic control. A particular substance, when it reaches a given concentration in the body, reacts to stop its own production until its concentration falls below a critical point. Then the process starts again to meet the organism's requirement for that substance. This process enables a living creature to conserve energy, and raw materials, and to avoid storage problems. This enzyme control system, discovered in bacteria, and now known to occur in birds and mammals, has usually been studied in terms of discovering which substance checks which enzyme.

John C. Gerhart and Arthur B. Pardee (formerly of the University of California, Berkeley, and presently at Princeton University) have tried to uncover this process in the bacterium *Escherichia coli*. Carbamyl aspartate (CA) is the first step in a chemical pathway which leads to the production of cytidine triphosphate (CTP). So long as the bacterium removes CTP by building it into nucleic acids, the enzyme aspartate transcarbamylase continues its work of making CA. As soon as there is an excess of CTP, the enzyme is halted in its work without permanent loss of its catalytic ability.

To illustrate the way this biological thermostat works, Gerhart and Pardee have produced evidence that the enzyme molecule has two operational sites, one constructed to fit the substrates (necessary chemicals) of the first step (CA), and a second suited for the CTP. In this way an enzyme can bind specific sub-

stances of very different structure and electrical charge. The investigators believe their experiments show that when excess CTP forms, it is bound to the second site, and, in so doing changes the shape of the enzyme molecule so that the first site no longer fits its substrates exactly. As a result, the enzyme action is inhibited.

The authors call attention to the growth advantage which this feedback system gives the organism, and believe it arose by mutation in the process of evolution. Since enzymes control nearly every bodily reaction, knowledge of their operations is a prerequisite for understanding both health and disease.

The report appeared in the *Journal of Biological Chemistry* (237: 891-896).

TOOLS OF SCIENCE

MAKING ACTIVE BIOLOGICAL CELL PRODUCTS AIDED BY ULTRASONIC IMPROVEMENTS

Rapid changes of pressure in a liquid sound field produce ultrasound, which is usually accompanied by growth and violent collapse of vapor bubbles in the liquid. Ultrasonic methods are used to disintegrate cells in order to prepare some biologically active compounds. The violent collapse of the bubbles has been considered the most important factor in breaking cells, but the energy released when bubbles collapse may produce heat and the formation of free chemical radicals which can make some active compounds, such as enzymes, inactive.

D. E. Hughes of Oxford University, and W. L. Nyborg of the University of Vermont, found that a needle vibrating with too low sound pressure to form bubbles in fluid still caused turbulent motions whose shearing effects were sufficient to break several types of cells. The investigators thought that the addition of a controlled number of small bubbles would increase the turbulence and shearing action, but avoid the undesirable effects of large bubble collapse. They accomplished their aim by drilling minute holes in the end of a vibrating bar. Small bubbles grew from air trapped in the holes, and the resulting turbulence broke more bacteria than was accomplished by a polished needle vibrating considerably faster and making large collapsing bubbles.

The new perforated bar and better understanding of ultrasonic principles should improve the production of enzymes and other biologically active materials. Hughes and Nyborg have already used this technique to break large molecules such as DNA (deoxyribonucleic acid) into active components. They believe further study of controlled disruption may tell us more about the structure of cells and the location of their enzymes.

This work was published in *Science* (138: 108-114).

FLYING SPOT MICROSCOPE MEASURES AND RECORDS VOLUME RELATIONS IN CELLS

Joseph G. Hoffman of the University of Buffalo, New York, reported the use of the flying spot microscope to measure the volume of nuclei in relation to the volume of cytoplasm in intact tumor cells. This size ratio may be one of the indications of cell age, since older cells are thought to have proportionately larger nuclei.

Dr. Hoffman's flying spot microscope is designed to view and record 600 lines per scan per second. The instrument enables an investigator to view the field, searched with an oil immersion lens, from a 12-inch television tube and to hand-select any field or any line in the field if he wishes. He may also adjust the size of the field manually. The measurements are taken by oscilloscope photography, and the amounts may be put on paper or magnetic tape using the Fortran program for data processing so that a computer can digest the results quickly.

This instrument has been previously used by Box and Freund, and has been improved by Hoffman who is working on further refinements. The great advantage offered by this microscope, besides its speed and recording features, is a method for the study and measurement of relationships within intact living cells without having to kill or disrupt them.

Variants of this type of microscope have already been used for counting bacteria, to study brain injury, and in blood studies where a large number of cells must be observed, differentiated, and recorded. The computer-microscope combination should be helpful in growth, aging, bacteriological, neurological, cancer, and biological research.

A description of the microscope and some of the theory of its operation was reported in the *Annals of the New York Academy of Sciences* (97 (art. 2): 380-394).

BIOLOGICS STANDARDS

WITNESSES

DR. RODERICK MURRAY, DIRECTOR, DIVISION OF BIOLOGICS STANDARDS

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS, NATIONAL INSTITUTES OF HEALTH

GEORGE A. BRUST, EXECUTIVE OFFICER, DIVISION OF BIOLOGICS STANDARDS

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	1,188	1,453	1,768
Positions other than permanent.....	16	19	19
Other personnel compensation.....	57	62	78
Total personnel compensation.....	1,261	1,534	1,865
12 Personnel benefits.....	124	149	184
21 Travel and transportation of persons.....	78	90	99
22 Transportation of things.....	6	6	6
23 Rent, communications, and utilities.....	24	33	34
24 Printing and reproduction.....	5	5	5
25 Other services.....	106	472	738
Payment to National Institutes of Health management fund.....	799	742	832
26 Supplies and materials.....	591	811	854
31 Equipment.....	42	105	170
Total obligations.....	3,036	3,947	4,787

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	206	265	297
Full-time equivalent of other positions.....	4	4	4
Average number of all employees.....	196	224	271
Number of employees at end of year.....	207	249	287
Average GS grade.....	6.9	7.4	7.4
Average GS salary.....	\$6,030	\$6,654	\$6,595
Average salary of ungraded positions.....	\$3,821	\$3,898	\$3,898

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
Biologics standards (program costs, funded) ¹ -----	3,060	3,947	4,787
Change in selected resources ² -----	-24	-----	-----
Total obligations-----	3,036	3,947	4,787
Financing: Comparative transfer from other accounts (-)-----	-3,036	-3,947	-----
New obligational authority (appropriation)-----	-----	-----	4,787

¹ Includes capital outlay as follows: 1962, \$53,000; 1963, \$105,000; 1964, \$170,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$111,000 (1962 adjustments, -\$2,000); 1962, \$85,000; 1963, \$85,000; 1964, \$85,000.

GENERAL STATEMENT

Mr. DENTON. Dr. Murray, do you have a statement?

Dr. MURRAY. Yes, sir, I have a prepared statement.

Mr. DENTON. All right, we will make your statement a part of the record, and you can summarize it for us if you will.

(The statement follows:)

Mr. Chairman and members of the committee: Since the Division of Biologics Standards is this year, for the first time, requesting a separate appropriation, a brief résumé of the events leading to the establishment of the Division might be in order.

BACKGROUND

The Federal Government's responsibility for the control of biological products began on July 1, 1902, when the Congress passed an act to regulate the sale in interstate commerce of all viruses, serums, toxins, and analogous products applicable to the prevention and cure of diseases of man. The statute, now a part of the Public Health Service Act, is basically the same as in 1902. At that time, the technical responsibilities of the biologics program were assigned to the National Institutes of Health, then known as the Hygienic Laboratory. In 1937, the Laboratory of Biologics Control was created within the then National Institutes of Health, and in 1948 it was made part of the National Microbiological Institute.

In June 1955, authority was granted the Surgeon General by the Secretary of Health, Education, and Welfare to expand the biologics control function of the Public Health Service to the status of a separate division within the National Institutes of Health—the Division of Biologics Standards.

THE DIVISION'S FUNCTION

The Division's primary function is to administer those provisions of the Public Health Service Act pertaining to the safety, purity, and potency of such biological products as vaccines, antitoxins, therapeutic serums, and human blood and its derivatives. These products are derived principally from pathogenic or potentially pathogenic microorganisms, and their preparation requires careful control. Experience has shown that such control can be accomplished most effectively within the context of an active research program which concerns itself with the problems at issue. Thus, the programs of the Division—both control and research—are product-oriented, and their scope, direction, and intensity are dictated by the need to provide essential information for the development of requirements and regulations for new biological products, as well as the continuous improvement of tests to insure the safety, purity, and potency of all such products.

The large-scale support which has been given to medical research in recent years is now beginning to be reflected in the development of improved methods of immunization and new therapeutic measures. The increasing public interest

in these discoveries, has, in turn, given competitive stimulus to hasten the development of new products. The time interval between research and product availability has been materially reduced. The Division, charged with the responsibility to develop standards for these products must, in turn, expand its own research, testing, and control efforts to obviate delay in determining whether such products meet licensing requirements.

IMPLEMENTATION OF FUNCTION

The control of biological products is based on a system of licensure. This system includes the issuance by the Secretary, DHEW, of both establishment licenses and product licenses, following determination by the Division that the prescribed standards for safety, purity, and potency have been met. These standards are set forth in regulations which are continually reviewed for adequacy and revised as scientific knowledge advances.

At the end of the calendar year, 195 establishment licenses and 1,253 product licenses were in effect, the latter covering 289 specific biological products. Determination of eligibility for licensing of establishments and of individual biological products is a major activity of the control program. Prior to licensing, the manufacturer's physical facilities must be inspected, his operating procedures observed, qualifications of his scientific and professional personnel reviewed, all data submitted with his application carefully evaluated, and representative samples of his product tested in the Division's laboratories.

Once a product is licensed, continuing surveillance is maintained through the periodic inspection of the manufacturer's facilities and production methods, review of his records of production and testing, and testing of representative samples of his product in the Division's laboratories. From December 1, 1961, through November 30, 1962, over 7,000 control tests were carried out to verify the safety, potency, and purity of licensed biological products. The results of these tests served as a basis for the release or rejection of the more than 5,000 lots of products submitted to the Division by manufacturers during this period. The testing of representative samples of these products requires the skills of trained professional personnel to carry out a variety of tests, ranging from relatively simple sterility tests to complex and costly potency determinations and safety tests.

The Division's research program plays a vital part in the development of standards and of control testing procedures for new and established biological products. In the search for meaningful and reliable tests from which can be developed criteria for standards for safety, purity, and potency, extensive research involving a large number and variety of animals is often required. Even after a product is licensed, the continuing testing of individual lots of the product before release requires extensive facilities, many man-hours, and large numbers and varieties of animals.

To assure that every lot of a product is of consistently acceptable and uniform potency, standard physical reference preparations are developed and distributed by the Division to manufacturers and to laboratories engaged in biologics standardization. Seventy-five such preparations are now maintained and approximately 6,000 vials are distributed annually to research and control laboratories of licensed manufacturers, health departments, and universities in this country and abroad.

Scientific personnel of the Division meet frequently with their counterparts in industry to discuss matters of mutual scientific and technical interest. In addition, conferences are held with technical representatives of individual manufacturers concerning testing problems and production difficulties peculiar to their own organizations which might affect the safety, purity, and potency of their products. Through such cooperation with industry, as well as with independent investigators throughout the country, the Division is frequently able to identify potential problem areas in production and control before serious difficulties can arise which may affect the quality or availability of licensed biological products.

Because of its regulatory responsibilities, the Division must be prepared on short notice to invest heavily, both in man-days and in dollars, in enforcement activities. On the basis of findings uncovered during routine inspection and surveillance, Division scientists conducted an extensive investigation of irregularities in the processing and distribution of blood and blood plasma in the New York area last year. An indictment was later returned by a Federal grand jury in Manhattan on charges of changing the labels on containers of outdated human

blood. This year, the investigation and other procedures connected with these cases continued to call for the expenditure of the Division's time and resources.

In addition, problems often arise concerning long-established products. Thus, a continuing and active interest must be maintained in areas of research which are no longer of primary interest to scientists working in a particular scientific field, as for example, smallpox and the rickettsial diseases. This function is of considerable concern and responsibility for the Division in fulfilling its mission.

LIVE POLIOVIRUS VACCINES

The newly developed products, however, have created the heaviest and most urgent demands on the Division during the past year. Complex problems have emerged in the process of evaluating the results of widespread use of the live poliovirus vaccines. While these problems were largely epidemiological, the extent of the related laboratory studies carried out in relation to these problems indicates that it will be necessary for the Division to devote increased effort to testing and to research on control methodology of candidate products of these and similar types.

Types 1 and 2 of the Sabin strains of the live, oral vaccine were licensed during the fall of 1961. The delay in the licensing of the type 3 strain—genetically the most labile of the three strains—was related to difficulties encountered under manufacturing conditions in the production of five consecutive lots of vaccine which would meet the requirements for a low degree of neurovirulence in monkeys, as well as specific characterizations required in tissue culture tests.

The monkey neurovirulence tests required for all three types of live poliovirus vaccines involved extensive studies. More than 150 neurovirulence tests have been made in more than 4,000 monkeys since the first vaccine samples were submitted to the Division for testing by the manufacturers. This testing has provided a wealth of information and experience that is invaluable in judging the validity of individual tests.

The Division has also been concerned with the development of (1) satisfactory methods for determining virus titers, that is, the measurement of the amount of virus in the vaccine, and (2) adequate procedures for examining vaccine lots for the presence of adventitious agents, such as SV-40.

MEASLES VACCINES

In the development of requirements for measles vaccine, the Division has drawn on its experience with other vaccines grown in tissue culture, the most comprehensive of which was with the poliomyelitis vaccines. However, since each virus has its own characteristics, and the properties of live vaccines depend on such factors as how the vaccine virus enters the body, where it proliferates, and what element—mechanical, physiological, immunological, and virological—favor or inhibit its ability to "take," one vaccine is not truly comparable to another.

In addition to the problem associated with all tissue culture-producing vaccines, development of regulations for measles vaccines called for an extensive array of controls since there are three products involved—live measles vaccine, inactivated measles vaccine, and standardized gamma globulin for use with the live vaccine.

First, recommendations based upon the best technical information available were developed relating to the manufacture and control of these products; second, regulations were developed for publication as a notice of proposed rule-making with invitation for public comment; and third, final regulations were drawn up for the production and testing of these products.

The regulations cover the characteristics of the measles virus strains to be used in the vaccine; the exclusion of adventitious agents from the virus fluid used in manufacture; the employment of a variety of animal and tissue culture test methods; the demonstration of satisfactory clinical use of the vaccine, including clinical effectiveness; and the stability of the live virus vaccine strains in terms of capacity to revert to significant virulence in man.

As with all new biological products, the information most difficult to obtain concerns the stability of the product under conditions of actual use, yet without this information a realistic dating period cannot be set.

An important need in the testing of measles vaccine is a supply of monkeys that are susceptible to measles virus. While monkeys are susceptible to measles infection, they are not exposed to it under natural conditions. However, dur-

ing procurement and shipping, they readily develop an imperceptible measles infection on contact with infected monkeys or human beings. As a result, almost all of the animals have developed resistance to measles infection by the time they reach the laboratory. This renders them unsuitable for many of the tests required in the evaluation of the vaccine. Therefore, special procurement, handling, and transportation of these animals are essential, as well as special quarantine and conditioning requirements prior to and during their use in measles vaccine studies. This same finding may well apply to the testing of viral vaccines of the future. For example, should a vaccine for infectious hepatitis evolve, chimpanzees might be used as test animals since there is some indication that these animals may be susceptible in contrast to other laboratory animals, including monkeys, and the same requirements for their handling would obtain.

ADVENTITIOUS AGENTS

A difficult problem encountered in working with tissue culture-produced vaccines is the occurrence of adventitious viruses, many of them previously unknown. Their presence in the tissue cultures used for production of viruses represents a complicating factor in production and testing procedures. Since their role in the cause of human disease is rarely demonstrable, the only course to pursue is to exclude them from the final product insofar as is possible with available testing methods.

Experience with one such simian virus, SV-40, sharply emphasized the problem of viruses that are unidentifiable by tests normally employed. Although no relationship of SV-40 to the development of human disease has been demonstrated, this virus is associated with the production of tumors when inoculated into baby hamsters and, under certain conditions, tissue cultures infected with the virus show changes that suggest a tumor-producing potential. In order to insure that this adventitious agent would be excluded from commercial vaccines, new methodology was developed and adequate test procedures were designed as a result of extensive research conducted by Division scientists.

The production of measles virus in chick embryo tissue culture also presents a problem since a number of adventitious agents are known to be present in fowls. Although vaccine produced in the developing embryo of the hen's egg is well tolerated by human beings as demonstrated by the large-scale use of yellow fever, typhus, and influenza vaccines for more than 20 years, analogous experience with chick embryo tissue culture is limited.

One approach toward the resolution of some of the testing problems encountered with adventitious viruses is the development of continuous cell line tissue culture preparations which would obviate the use of primary cell cultures. Such a cell line has been initiated by the Division using kidney tissue of the African green monkey. The cell line is in its 125th passage and its continuous growth is considered to be established. These cells have not changed their sensitivity to SV-40 virus, and are sensitive to attenuated measles virus as well as a variety of other viruses.

INFLUENZA VACCINE

During the past year a number of variants of the influenza virus strains have appeared in this country. In cooperation with other interested laboratories, the Division has paid close attention to these variants with a view to the possible selection of an additional virus strain for inclusion in the vaccine now in use. The last change was in 1957 when the Asian strain of influenza virus spread throughout the world. By December 1962, it appeared that the incorporation of new strains in the vaccine would again be called for and appropriate studies were initiated by the Division in cooperation with manufacturers and specialists in this field.

BLOOD PRODUCTS

Broad-based, comprehensive research directed toward the improvement of testing procedures for the control of biological products derived from blood are being continued in the Division's laboratories. These studies include research on freezing, storage at various low temperatures, thawing and drying of the many elements of whole blood, and the protein fractions of plasma.

Presently, there is much interest in the components of the blood coagulation system. Some of the potential products under study show immunological or biological activities for which there are no established test criteria. Research is being carried out on some of the fundamental characteristics of the coagulation components in order to obtain information on which to base control tests.

MULTIPLE ANTIGENS

Industry continues to attempt to meet the demand by the medical profession for multiple antigens that will immunize against several diseases simultaneously, although the preparation of these products is a complex process. This is especially true of the quadruple antigen vaccine which is used for pediatric practice. This product is composed of diphtheria and tetanus toxoids and pertussis (whooping cough) and poliomyelitis vaccines. Studies conducted by the Division on the stability of this product revealed that there was a significant decrease in the potency of the pertussis component during the prescribed dating period. The reasons for this are, as yet, obscure. However, as a result of the investigations, the dating period for this product was shortened and the potency requirement of the pertussis component increased in order to insure that the potency of the pertussis component does not fall below the required minimum level even when the product is exposed to variable market conditions.

BIOCHEMICAL STUDIES

The Division is now devoting increased attention to the biochemical and biophysical aspects of virology—an area in which many new discoveries of basic importance in the prevention and control of infectious diseases may be expected to emerge. Advances in recent years in the field of virology have focused attention on the role of the nucleic acids, not only in the field of virology, but in the entire field of biology.

COOPERATIVE RESEARCH WITH OTHER COUNTRIES

Experience has shown that answers to health problems in the United States can often be more readily investigated in other parts of the world. Two such potentials are presently being pursued by Division investigators in cooperation with workers abroad.

A study in west Africa is adding materially to our knowledge of the use of live attenuated measles virus vaccine. The project, undertaken as a collaborative venture by the Division, the Ministry of Health in Upper Volta, and the Agency for International Development, has demonstrated that, despite the difference in environment and greater vulnerability to natural measles infection, west African children respond to live measles vaccine in a manner similar to American children.

In New Guinea, a study has been undertaken by the Division in cooperation with Australian workers concerning the prevention of tetanus in the newborn—a serious cause of death among the newborn in that area—by prior immunization of the mothers.

During the year, more than 100 scientists from foreign countries have spent from 1 day to several months in Division laboratories studying and comparing methods of testing and control of biological products.

Division scientists continue to serve as members of international study groups in the World Health Organization's program for the development of international uniformity of biological products.

PROGRAM PLANS

This next year will be the Division's first year of operation under a separate appropriation. Growth in responsibilities is reflected by various increased needs in research and control areas.

For 1964, we are requesting \$4,787,000, an increase of \$840,000 over the 1963 appropriation of \$3,947,000.

Although laboratory space, including quarters for experimental animals, appeared adequate when the present Biologics Standards building was planned, requirements for new programs, particularly live poliovirus vaccine and measles vaccine, have increased considerably. Funds have been made available for planning for a new annex to the present Division facilities, and architectural plans are being developed. Until the annex is available, the Division will temporarily house its overflow in rented space, if necessary.

In 1963, the Division initiated two programs—research contracts and data processing. It is anticipated that many of the 1963 research contracts will be renewed and as the results from the initial contracts uncover leads worth exploring in depth, the program will expand. An increase of \$200,000 is requested for this purpose. For data processing, an increase of four positions

and \$69,000 is requested to further develop a system for collecting licensing, control, and testing data and to assist the Division's Chief of Statistics in the performance of essential analyses.

Experience with the continually increasing number of licensed blood banks has demonstrated the need for more thorough and detailed inspection. The number of inspectors presently available limits the amount of time that can be spent on each inspection. A staff increase of five and \$75,000 is proposed as a first step toward increasing the time devoted to the inspection of each licensed blood bank.

Recent progress in the field of allergens has shown the need for additional personnel trained in botany as research in the field of pollens and other allergenic material of plant origin expands. In addition, there is a need for additional study of BCG vaccine and other bacterial vaccines, and investigation of the effect of enzymes on the potency stability of bacterial products. An increase of five positions and \$41,000 is requested to strengthen the staff for these purposes.

The Division proposes to further expand its virus research program, including the arboviruses, to meet research needs including tissue-culture work, pathology requirements, and animal research, and is requesting four positions and \$72,000 for this expansion.

The Division is requesting four positions and \$38,000 in order to devote greater attention to the biochemical and biophysical aspects of virology—an area in which many new discoveries of basic importance in the prevention and control of infectious disease may be expected to emerge. Formalization of the program initiated in 1963 to centralize the direction of the inspecting, licensing, and control testing functions of the Division will require the addition of an Associate Director for Control with three supporting staff and \$42,000, as well as the enlargement of the administrative office staff by six positions and \$33,000.

Increases for mandatory items such as the cost of the pay raise and postal rate increases, annualization of new positions authorized in 1963, 2 extra days' pay, and annualization of the commissioned officers' quarters allowance increase amount to \$180,000.

The increase of \$90,000 in payment to the National Institutes of Health management fund is this Division's proportionate share for centrally furnished services.

Dr. MURRAY. Mr. Chairman and members of the committee, the Division of Biologics Standards this year is requesting a separate appropriation in line with the wishes of the committee. Formerly we had received our funds from the "General research and services" appropriation.

RESPONSIBILITIES OF DIVISION

The Division of Biologics Standards is responsible for administering the biologics control provisions of the Public Health Service Act. In support of its control activities, it conducts an active research program designed to furnish data upon which regulations can be based, adequate testing procedures developed, and physical reference preparations produced and supplied.

The large-scale support which has been given to medical research in recent years is reflected in the expanding development of new methods of immunization and therapy. The application, particularly, of new tissue-culture systems, to vaccine production and the recent widespread interest in live vaccines has complicated and expanded the testing procedure required for such products. The concern of both the scientific community and of the public over the role of viruses in the production of tumors has placed greater emphasis on the exclusion of adventitious animal viruses from tissue-culture-produced vaccines.

Developments during the past 2 years have required additional attention to inspection, surveillance, and enforcement activities. Because it has become apparent that this increase in emphasis in these responsibilities is not of a temporary nature but rather is representative of a continuing trend in biologics control, the Division has plans to expand its investment in this area and to strengthen and consolidate the direction of these activities.

Although newly developed products have created the heaviest and the most urgent demands on the Division during the past year, problems often arise concerning long-established products. For this reason, the Division must continue to maintain an active interest in areas of research which are no longer of primary concern to scientists working in a particular scientific field.

INCREASE REQUESTED FOR 1964

In conclusion, Mr. Chairman, the request for the Division of Biologics Standards is \$4,787,000, as compared with \$3,947,000 available in 1963.

Mr. DENTON. Thank you.

As you have stated, the amount available for 1963 is \$3,947,000, and the amount requested for 1964 is \$4,787,000, which is an increase of \$840,000 and 32 positions. Is that right?

Dr. MURRAY. That is correct.

INCREASE FOR RESEARCH CONTRACTS

Mr. DENTON. \$200,000 of the increase is for research contracts. This program was just started this year, was it not?

Dr. MURRAY. Yes, we started this this year; that is right.

Mr. DENTON. Would you describe the program, and tell us how much you are spending this year?

Dr. MURRAY. The general intent of this program is to obtain information and data usually of a repetitive nature, which represents an extension of the kind of thing which we are called upon to do in our laboratories, but are unable to do on the scale required because of limitations of space at the present time.

The types of projects which are under consideration are, for instance, the preparation of chemical compounds, such as can be used in poison ivy standardization. This is being done under contract, and would be evaluated, in our division, as a means of bringing improved standardization procedures to this particular product.

Other examples are contracts to obtain optimum standards of potency for blood grouping serums, which represents a great deal of repetitive testing, and, upon the basis of this information, the division will be able to improve its control procedures and requirements for these kinds of products.

In addition, there are a variety of reagents which are required in testing which need the facilities existent in outside laboratories, and it would be wasteful of time and valuable laboratory space within our division to produce these.

For instance, we are seeking to obtain anti-human protein serum for use in some of the testing programs for blood products. These are just some of the ideas, some of the things which are incorporated in such a program.

NEED FOR BUILDING EXPANSION

In this regard, we anticipate that there will be favorable consideration given to the addition of an annex to the present building. This should be available in approximately 3 years' time if approval for these requests is granted. The idea here is this: in the meantime these proposals for research will bridge the gap between the needs of the present and what will be available when such construction is completed.

Mr. DENTON. We just built the new building for Biological Standards, did we not?

Dr. MURRAY. Mr. Chairman, the original plans for this building were initiated approximately 7 years ago.

Mr. DENTON. When was it completed?

Dr. MURRAY. It was completed 2 years ago, but—

Mr. DENTON. You need to build an addition to it already?

Dr. MURRAY. That is correct.

Mr. DENTON. What was the trouble? Why were not the original plans adequate? Or just what was the reason why we need to have this addition built within 2 years?

Dr. MIDER. The original plans were adequate at the time we drew them up, but we had no appreciation of the number of new products that would come up under the jurisdiction of the Division of Biologics Standards at that time, or the tremendous problems that some of these would create.

At this time, I believe Dr. Murray's organization is using 5,000 monkeys a year, largely in the control of vaccines, such as poliomyelitis vaccine.

We have a vaccine research program in the Allergy and Infectious Diseases Institute for prototype vaccines. If they are successful, they will ultimately have to be licensed and controlled by the Biologics Standards.

The hepatitis-type vaccine is being developed away from the National Institutes of Health. There is substantial progress in the whole field of allergy. Poison ivy, as Dr. Murray pointed out, is assuming increasing importance. We may be able to control the uncomfortable skin reactions.

This division, with its control activities, can never let go of a product once it is licensed for sale.

Mr. DENTON. Do you have people working outside of the new building now?

Dr. MURRAY. No. Except in connection with animal activities, physically outside the building.

The requirements for laboratory space are such that we are confined to the facilities which we have within the building.

Mr. DENTON. How far along are you in planning this annex?

Dr. MURRAY. We are actually working with an architect-engineering firm at the present time in development of plans. It is my understand-

ing that the request has been introduced in connection with the general building appropriation.

Mr. DENTON. You have no funds for that yet, but you have asked them for 1964?

Dr. MURRAY. That is correct.

INCREASES FOR INTRAMURAL PROGRAM

Mr. DENTON. How do you expect to use the increase you are asking for in 1964?

Dr. MURRAY. We can give you this information very briefly:

The increase requested in 1964 amounts, as we have said, to \$840,000. As far as direct operations are concerned, the amount involved here is \$570,000; \$72,000 of this is being requested in connection with the further development of our virus programs, and \$41,000 for investigation of allergenic and bacterial products. This includes additional work in connection with the better standardization of such things as poison ivy, which I mentioned, tuberculin, and work on old established vaccines like cholera vaccine and typhoid vaccine, which have come into prominence during the past few years because of a better demonstration of the efficacy of certain preparations under advantageous conditions abroad. The amount of \$75,000 is requested to increase the time available for inspection of each licensed blood bank and \$38,000 is requested for expanding our work on the biochemical and biophysical aspects of virology.

Additionally, \$144,000 is requested for expansion of the administrative functions of the division. This includes licensing operations, the inspections of licensed establishments, infringements of the provisions of the act, and so forth. It also includes work designed to adapt data processing methods to the handling of the vast ocean of data and information which is enveloping us at this time, and as you have mentioned, sir, \$200,000 for research contracts.

Mr. DENTON. Yes. In that connection, all your work is intramural except that \$200,000 for research contracts; is it not?

Dr. MURRAY. That is correct.

REASONS FOR NO GRANT ACTIVITY

Mr. DENTON. Why could not some of this be handled as a grant program?

Dr. SHANNON. Mr. Denton, could I comment on that?

Mr. DENTON. Yes.

Dr. SHANNON. The basic fundamental science background for grants programs is in the scientific community across the board through grants, but this is a basic Federal control responsibility. The information upon which Federal control actions are taken must be derived officially within the organization that exercises the control function. So one is very limited here in the amount of work or the amount of help one can get from outside groups.

Now, Dr. Murray's staff must carry on some scientific exploration in parallel with their control activity in order to maintain a covey of top scientists to exercise control functions. But it is limited in scope and is not associated with extramural programs of comparable activities.

NEW POSITIONS REQUESTED

Mr. DENTON. You had, last year, 265 employees. You are asking for 297, which is an increase of 32. Now, what are these employees? Are they clerks, are they public health officers, or are they technicians? Just what is their classification?

Dr. MURRAY. I can go over these briefly with you, sir.

Mr. DENTON. Would you rather put it in the record?

Dr. SHANNON. That is summarized in terms of the areas of activities on pages 71 through 73. We would be glad to put the precise exhibit in the record.

Mr. DENTON. Let's put that page 73 in the record.

(The page follows:)

Biologics standards—New positions requested, fiscal year 1964

	Grade	Annual salary
Biologics standards:		
Scientist.....	GS-14.....	\$12,854
Statistician.....	GS-13.....	11,170
Scientist-4.....	GS-12.....	37,940
Statistician.....	GS-11.....	8,050
Administrative officer-2.....	GS-9.....	13,354
Scientist-3.....	GS-9.....	20,081
Clerical assistant.....	GS-7.....	5,554
Statistician.....	GS-7.....	5,554
Clerical assistant.....	GS-5.....	4,576
Research technician-3.....	GS-5.....	13,728
Clerical assistant-4.....	GS-4.....	16,472
Research technician-2.....	GS-4.....	8,236
Clerical assistant-2.....	GS-3.....	7,654
Research technician-3.....	GS-3.....	11,481
Director grade.....	CO.....	13,320
Senior grade-2.....	CO.....	19,920
Total new positions, all activities-32.....		209,894

Mr. DENTON. I presume these new employees are going to perform the duties that you enumerated in the request for increased appropriation, are they not?

Dr. MURRAY. That is correct.

CENTRALIZING LICENSING AND CONTROL ACTIVITIES

Mr. DENTON. Now, what is this program initiated this year to centralize the direction of inspection, licensing, and control testing activities? Page 71 of the justifications.

Dr. MURRAY. I might say that this question of improving and centralizing the licensing and control activities represents an effort to pull in from the various components of the division a number of functions which have been handled by some of the workers in those areas and having placed this in the office of the director of the division to give better control of the operation.

The method of control of biological products that the division applies is basically that of licensing biological products. Two kinds of licenses are issued. These are issued by the Secretary of the Department, but the recommendations come up from below. One is the license for the establishment itself; the other is a license relating to the particular product.

As time has gone on, the amount of effort, work, both administrative and laboratory, in connection with the license and review of products, has become tremendously extensive. It is no longer feasible to maintain the administrative and the laboratory activities down at the bench level as has been possible in the past.

We are attempting now in this proposal to strengthen this activity by centralizing the administrative aspects and leaving the more technical and scientific aspects within the laboratory.

COORDINATION WITH FOOD AND DRUG ADMINISTRATION

Mr. DENTON. How do you work with the Food and Drug Administration on this?

Dr. MURRAY. The Food and Drug Administration operates under different laws. The law which we operate under is within the Public Health Service Act and it covers the specific products which are for the most part in the nature of vaccines and serums, and subject to the licensing process.

We work reciprocally with the Food and Drug Administration because certain of the laws apply to all drugs; under certain circumstances, licensed biological products are excluded.

Mr. KELLY. In the exercise of the new drug act, as I understand it, if the substance is considered to be a biologic, Food and Drug Administration does not exercise its responsibilities there but the Public Health Service does.

Dr. MURRAY. If the product is licensed under the Public Health Service Act, then it is not subject to the new drug requirements of the Food and Drug Act.

COST OF VIOLATION INVESTIGATIONS

Mr. DENTON. How much of your total resources are devoted to investigation of violations or suspected violations?

Dr. MURRAY. This is a rather minor part at the present time. I think we can give you the exact figure.

Mr. BRUST. Last year, we spent \$30,000; this year we have spent \$16,000 so far. Exclusive of personnel.

Dr. MIDER. Mr. Chairman, may I point out no litigation was brought under the part of the Public Health Service Act relating to the Division of Biologic Standards until the year before last.

That is right, is it not?

Dr. MURRAY. Yes.

Dr. MIDER. This portion of the act originated in 1902.

Mr. DENTON. Are you sure you are right about that, you only spent \$30,000 investigating violations, or suspected violations?

Mr. KELLY. I think he said these were all exclusive of personnel time engaged.

These are out-of-pocket costs that were associated with this, exclusive of the personnel costs, those figures he gave you.

Mr. DENTON. I would think that would all be personnel. What else would there be but personnel investigating violations or suspected violations?

Mr. BRUST. Basically travel costs. There are in some cases costs of supplies and analytical costs for—

Mr. DENTON. You are not including personnel in there?

Dr. MURRAY. The staff of the division has been used for this.

Mr. DENTON. The what?

Dr. MURRAY. The normal staff of the division has been used for this purpose.

Mr. DENTON. Well now, as I get it, you spent \$30,000 last year on traveling expense and for some supplies in investigation of violations and suspected violations, but you do not have a figure on how much personnel costs were for this work.

Mr. KELLY. Accounts are not maintained that way, Mr. Denton. I think we could supply for you an estimate of the amount of effort that went into that, and the approximate cost of that.

Dr. MURRAY. We would be glad to provide it.

(The information follows:)

Division of Biologics Standards—Estimated costs of investigation of violations or suspected violations

	Fiscal year 1962	Fiscal year 1963 ¹
Travel.....	\$21,500	\$9,000
Other.....	8,500	7,000
Personnel.....	35,000	15,000
Total.....	65,000	31,000

¹ Through Feb. 28, 1953.

RECENT VIOLATIONS

Mr. DENTON. What significant case of violations have you discovered during the last year?

Dr. MURRAY. There are two that are currently pending trial. One of these concerns a broker of blood who was infringing or was alleged to be infringing the law by updating the blood.

Normally blood for transfusion has a dating period of 21 days. It must be used within 21 days or be rejected. The violation in here involved supplying blood which had gone beyond the period which was prescribed in the regulation.

The other operation was the unlicensed production and sale of human plasma.

Mr. DENTON. Of what?

Dr. MURRAY. The unlicensed production and sale of human plasma, which is a product which comes within the purview of this act.

Mr. DENTON. If there are any other important cases, you want to put in the record, of course you can do that.

Dr. MURRAY. We have none.

PROBLEMS OF LIVE POLIO VACCINE

Mr. DENTON. Do you have any particular problems with live poliomyelitis vaccine?

Dr. MURRAY. Also commonly called the Sabin vaccine.

Mr. DENTON. Do you have any problems with the live polio vaccine?

Dr. MURRAY. To be correct, I must say that we do have problems with it, because we are concerned with such products all the time.

I would like to point out this is an excellent example of the necessity for a large-scale scientific operation in the control of a biological product, because every lot produced has to be treated as a separate entity and tested as such.

This is in contradistinction to some drugs which are chemical in nature and that can be defined on the knowledge of their composition.

There have been some problems raised during the past year in connection with live poliomyelitis vaccine, but I believe that these have been resolved as a result of the activities of the Public Health Service as a whole. Live poliomyelitis vaccine is available on the market and recommended for use by physicians.

Mr. DENTON. Every batch or lot that is produced has to be investigated by you?

Dr. MURRAY. That is correct.

Mr. DENTON. I would think you would have a number of men assigned to that duty.

Dr. MURRAY. We do. About 50 percent of our activities, sir, are in connection with virology.

INVESTIGATIONS OF BCG VACCINE

Mr. DENTON. Now, on page 71, you say "there is a need to increase investigations of BCG vaccine." Would you expand on that statement, please?

Dr. MURRAY. BCG vaccine is an old established product. I believe there is one licensed establishment in this country. But we have felt for some time that there was a need for an improved scientific and control program within our own organization in order to be better aware of the quality and freedom from harmful effects of BCG vaccine.

This, as you know, is a live vaccine designed to be used in the prevention of tuberculosis.

Mr. DENTON. Has it been successful?

Dr. MURRAY. There are a number of views on that, and, in general, yes, it has been successful.

Mr. DENTON. It seems to me they told us one time it was not recommended for general use.

Dr. TERRY. There is a great deal of professional opinion, Mr. Denton, as to its usefulness in this particular country, in the United States, in terms of the approach to the control of tuberculosis. It is still used to a fair extent by some of our physicians, particularly in individuals and groups which are a high risk, such as, for example, student nurses and persons working around tuberculosis hospitals.

MEASLES VACCINE

Mr. DENTON. Do you want to say anything about the measles vaccine?

Dr. MURRAY. Yes, I will be very glad to.

This is a vaccine or group of vaccines which has been under development for some years now, ever since the measles virus was originally isolated by Dr. John Enders.

Mr. DENTON. What year was that?

Dr. MURRAY. That was in 1954.

I might say in passing that in many instances, when a virus which causes disease has been isolated and identified and can be grown in the laboratory, then the possibility of a vaccine is imminent.

This was true in the case of measles vaccine. However, the initial studies with the measles virus were rather discouraging. It could not be grown in sufficient quantities and the materials that were produced were unstable, did not retain their activity for more than a few days. But with the advances in tissue culture methodology during the past few years, the virus has been grown in quantity. It has been attenuated successfully to the point at which it produces only a mild illness in some human beings.

We have now the possibility of two vaccines, one a live vaccine which was actually developed by Dr. Enders himself, and the other is a "killed" vaccine using measles virus but inactivated in a manner analogous to the preparation of the Salk vaccine.

We anticipate vaccines of both types will be available in the next few months.

INFLUENZA VACCINES

Mr. DENTON. What about influenza vaccines?

Dr. MURRAY. Well, influenza vaccine is an old-established vaccine in the sense that it came into use, first of all, experimentally in the early 1940's. It has been used ever since that time and especially since the emergence of the Asian strain of influenza, now called the A-2 strain, in 1957.

One of the peculiarities about influenza viruses which is not shared by polio and other viruses that we have to deal with is that periodically it changes itself so that a vaccine which may have been useful against a particular strain may now no longer protect against it.

This is what happened with the Asian strain in 1957. As soon as that strain was isolated and studied—first isolations were made by military personnel in the Far East—it was very clear that it had such characteristics that the vaccine available at that time would not protect against that particular strain. During 1957, the strain that was isolated was adapted and introduced into the vaccine and has been incorporated in it since that time.

WORK ON VACCINES FOR COLDS

Mr. DENTON. Do you have any vaccine for common colds as yet?

Dr. MURRAY. I would not be facetious about that, but the common cold is not a definable, single illness. It is probably something which is caused by a great variety of agents, some of which we know.

Mr. DENTON. Well, I thought when I was out at the NIH that they were working on a vaccine for the common cold.

Dr. MIDER. I believe Dr. Andrews will be ready to testify in detail on that.

I can tell you one prototype vaccine, one of the very first to come out of this program, unfortunately produced no antibodies in man. But, remember, this was also true of measles at the beginning.

(Discussion off the record.)

NEED FOR ADDITIONAL SPACE

Dr. MURRAY. If I might just interject at this point, as a followup to what Dr. Mider said, I think this illustrates the problem that the division faces over the long haul and one of the reasons why this request for additional space came in. That is, we have to remain in a position of preparedness as new vaccines are developed. Here we have a group of respiratory disease vaccines in the course of rapid investigation and development, and we feel reasonably sure that if these are successful, there will be a demand for their use. Our Division has to be ready to step in with the necessary methodology for control and testing without any delay in order that the best public interest be served.

Mr. DENTON. Yes. Of course my only thought about that laboratory is there was not much foresight when we planned it.

Dr. MIDER. That is right.

Mr. DENTON. It is rather unusual to have to build an annex to a building that is 2 years old.

Dr. MIDER. Mr. Denton, may I agree with you, but point out this is one result of the farsightedness of your committee in supporting medical research through grants and through intramural operations.

At the time that building was planned, we could not identify very many viruses that would be associated with undifferentiated respiratory infections. Only a few years ago we were up around 25 percent; now it is 65 percent.

Mr. DENTON. I think that is very remarkable.

Dr. MIDER. It moves very rapidly.

Mr. DENTON. I think that is very remarkable.

The clerk of the committee called attention to the fact that the food and drug building is being built, and is already too small before it has been completed. So I guess this is not as bad as some others.

COOPERATIVE RESEARCH WITH OTHER COUNTRIES

You might tell us about your cooperative research with other countries. That will be my last question.

Dr. MURRAY. Yes, sir. We have mentioned this because these are studies which are carried on as a direct operation in order to gain experience with new products or else to exploit special opportunities which exist in connection with older products.

We have mentioned two main ones. At the present time, there is one being concluded in west Africa, particularly in the country of Upper Volta. This is a study that was initiated 1 year ago to try and see whether measles vaccine could be administered to children of that region of the world, because it was known that measles was a cause of a great deal of mortality. In fact, it has been estimated that in some of those countries of west Africa, 40 percent of the mortality between the ages of 1 and 5 years may be due to measles.

We did not know whether measles vaccine would be satisfactory, used in such a population, because they have a different cultural background, a different disease background, and a different nutritional background.

This study was initially undertaken at the specific suggestion of the Minister of Health of Upper Volta and proved that vaccination

was feasible. This was followed, during the past year, by a much larger study using experimental vaccines, not the final vaccines which will be used generally in this country when they are licensed, in order to see in a country like that—where, once measles vaccine does become commercially available, it certainly will be used because of the high mortality rate—whether it is feasible and possible to eradicate measles by a large-scale administration. As far as was possible, all the children between the ages of 6 months and 5 years were inoculated with measles vaccine and this has just been concluded. A total of over 700,000 doses have been administered successfully, and we are looking to the present measles season to see whether this is being effective.

Initial information is that no measles has occurred in those who received the vaccine, whereas in neighboring communities it has.

We also mentioned a rather minor study but one which is particularly important. This is in cooperation with some interested Australian physicians studying tetanus antibodies in pregnant women, in New Guinea for the most part. Tetanus is common there and the mothers apparently infect their children at childbirth.

We have not participated in any travel or any actual engagement locally in this affair, but use our resources. We are one of the few in the United States really set up to do this, namely, to measure tetanus antibodies in human serum.

And then I might mention just in passing that we regard as one of our continuing activities cooperation with the World Health Organization in its attempts to develop biological standards.

Mr. DENTON. Thank you.

Dr. TERRY. Mr. Denton, may I add something in connection with the Upper Volta study.

Dr. Murray mentioned that an experimental vaccine was used in Upper Volta. I would like to point out that at the same time similar, in some instances identical, experimental vaccines have been used in this country.

Dr. MURRAY. Oh, yes.

Dr. TERRY. In the field studies which are basically necessary to proving that the vaccine is a suitable product for licensure. So that in effect we were not doing anything in Upper Volta we were not also carrying out in this country.

The work we were doing there gave us a great deal of basic information which was essential to our knowledge for licensing of the product.

Mr. DENTON. Mr. Lesinski.

Mr. LESINSKI. No questions, just one comment.

(Discussion off the record.)

Mr. LESINSKI. Thank you.

Mr. DENTON. We thank you very much, gentlemen. We will adjourn until 10 o'clock Tuesday.

HIGHLIGHTS OF PROGRESS IN RESEARCH ON BIOLOGICS, 1962

ITEMS OF INTEREST ON PROGRAM DEVELOPMENT AND RESEARCH STUDIES CONDUCTED BY THE DIVISION OF BIOLOGICS STANDARDS

The accelerated pace of research in the area of infectious diseases has resulted in a significant increase in the number, complexity, and diversity of biological products. At the close of the calendar year, 289 such products were licensed under the provisions of the Public Health Service Act for commercial use in this country and abroad.

These products, which include the vaccines, antitoxins, therapeutic serums, and human blood and its derivatives, are developed for the most part from pathogenic or potentially pathogenic microorganisms. Their preparation requires careful control in order to minimize safety hazards which might occur in the course of processing, and to insure final products of satisfactory potency. Accuracy is essential in every step, for the end product is the preservation of human life.

Responsibility for the administration of these control measures resides with the Division of Biologics Standards. Effective administration requires the design and development, within a research context, of adequate and practical standards for the production and testing of biologics, careful surveillance of production methods, and the continuous improvements of testing procedures. Thus the control program of the Division is necessarily supported by an active and flexible research program in order to keep pace with the development of new and improved immunizing agents, to prepare physical references for these products, and to devise testing procedures for them once they are ready for commercial production.

The research programs of the Division's six laboratories—Bacterial Products, Biophysics and Biochemistry, Blood and Blood Products, Control Activities, Viral Immunology, Virology and Rickettsiology—include a diversity of projects, many of immediate practical urgency, and all having direct relation to the prime responsibility of the Division.

SEROLOGIC TESTS STANDARDIZED FOR MEASLES ANTIBODIES

Serologic tests for measles antibodies became feasible when Enders and Peebles demonstrated in 1954 that the virus could be cultivated in monolayers of human kidney cells. Two classical procedures of viral immunology—the complement fixation (CF) and the virus neutralization tests were employed by these workers. More recently, others have observed that erythrocytes from certain primates were agglutinated by fluids containing measles virus. Several groups have since described hemagglutination and hemagglutination inhibition (HAI), employing red corpuscles from a number of common monkey species.

Dr. Harry M. Meyer, Jr., and coworkers, Laboratory of Virology and Rickettsiology, have been concerned with the study of the several variables in the CF, virus neutralization, and HAI techniques, in order to develop methodology for uniform serological tests for measles vaccines.

The development of a standard measles neutralization test required the arbitrary definition of several constants. In each instance, the primary consideration was the election of a method that would be simple and give reproducible results. Elimination of variables from the CF test, although desirable, was not as critical a problem as standardization of the virus neutralization technique, for it is the neutralization test that serves to define the success or failure of each attempted immunization. Moreover, the use of this procedure in conjunction with the measles reference serum offers a method for accurate assay of measles-immune gamma globulin. The constant potency of this product is essential since it is used to prevent the natural disease, as well as to reduce the febrile reaction associated with the administration of live measles vaccine.

In a comparison of complement fixing and neutralizing antibody titers in a number of pediatric sera, Dr. Meyer found that, although the CF procedure could be used to advantage in rapid screening of sera for measles antibodies, it lacked the sensitivity of the more time-consuming neutralization test. (Reported in "Diseases of Children.")

More recently, studies of the HAI test with measles virus have shown this test also to be more sensitive than the CF test for use in serological surveys, diagnosis of recent infection, and antibody determinations subsequent to the immunization of children and monkeys with live measles vaccine. In addition, the HAI test possesses the advantages of speed and economy over the more tedious neutralization test. It is presently being used for antibody determinations in clinical studies with live measles vaccine and, as additional data become available, it may supplant the neutralization test for use in potency determinations of killed measles vaccine.

LIVE MEASLES VACCINE TESTED IN TROPICAL ENVIRONMENT

The safe and effective immunization of some 400 West African children with live measles vaccine was concluded early this year. The 2-month pilot study was conducted in Ouagadougou, Upper Volta, by Dr. Harry Meyer, Jr.; Dr. Daniel Hostetler, Jr.; and Mrs. Barbara Bernheim, Laboratory of Virology and Rickettsiology, at the invitation of the Minister of Health, Republic of Upper Volta. The vaccine used was the live attenuated Edmonston strain developed by Dr. John Enders and his group at Harvard University.

The study was made to determine whether the vaccine which has been administered safely to some 10,000 children in the United States would be equally safe for west African children in whom natural measles is characteristically associated with a high mortality. The disease is reported to kill 25 to 50 percent of children in Upper Volta during the first few years of life, as contrasted to 1 in 10,000 in this country.

No serious reactions were encountered in any of the 439 children given the vaccine, although most of them were suffering from 1 or more acute or chronic infections. The 683 children selected for the study had no previous history of measles. They were divided into three groups of approximately equal size. Group 1 received only the live attenuated measles vaccine; group 2 was given the vaccine followed by an injection of gamma globulin; group 3 got only gamma globulin, thus serving as a control to determine the incidence of non-vaccine-related illness in groups 1 and 2. Prior to vaccination, each child was given a complete physical examination.

Venous blood samples, taken from about half the members of each of the three groups prior to vaccination and 4 weeks later, were brought back to DBS laboratories for measurement of measles antibody content. Results of the serologic tests showed that 94 percent of the inoculated children were susceptible to measles prior to vaccination; all of those vaccinated had developed immunity when tested 4 weeks after inoculation. The level of measles antibody was slightly higher in those who received the vaccine without concurrent gamma globulin.

CONTINUOUS MONKEY KIDNEY CELL LINE ESTABLISHED

The extensive use of rhesus and cynomolgus monkey kidney cell cultures for the isolation, growth, and study of viruses has brought to light many hitherto unknown simian viruses. These viruses appear during incubation of cell cultures prepared from apparently healthy monkeys and make their presence known by their destructive (cytopathogenic) effect on the cells.

One of these simian agents is the vacuolating virus or simian virus 40 (SV-40), first isolated by Sweet and Hilleman in 1960 from rhesus monkey kidney cultures. SV-40 produces no obvious cytopathogenic change in rhesus or cynomolgus cultures, but regularly does so, with formation of characteristic cytoplasmic vacuoles, in tissue culture cells prepared from the kidneys of the African green monkey, *Cercopithecus aethiops*.

Since primary cercopithecus kidney cultures are used for diagnostic detection of SV-40, and since such cultures are occasionally contaminated with SV-40, an effort has been made to establish a virus-free continuous tissue-culture cell line which could be used as a laboratory tool in studies with SV-40. Such a cell line has now been established by Mrs. Hope E. Hopps and coworkers, Laboratory of Virology and Rickettsiology. (This work was presented at the Federation meetings in Atlantic City.)

The continuous cell line, designated BS-C-1, was derived from cultures of healthy primary cercopithecus cells and has been successfully carried through 74 serial passages. BS-C-1 cells grow readily in appropriate media when thawed after storage at -70°C . No difficulty has been encountered in shipping the cell line, and cultures have been established in more than a dozen laboratories, including two in England and one in Australia.

Sensitivity of the BS-C-1 line to infection with SV-40 has remained unchanged throughout 14 months of continuous cultivation. This is of particular interest since the chromosome number of the cells altered between the 20th and 40th passage, decreasing from a normal 60 to 58-59. BS-C-1 cells also permit growth of several other viruses, including attenuated measles virus; attenuated polioviruses 1, 2, and 3; respiratory syncytial virus; Riff Valley fever virus; and Dr. O'Malley's hepatitis isolate, A-1.

The ease with which the BS-C-1 cells can be grown, as well as their susceptibility to viruses other than SV-40, suggest that the line can be employed for laboratory use with a variety of viral agents.

TUMOR-INDUCING SUBSTANCE IN MONKEY CELL EXTRACTS IDENTIFIED AS SV-40

In May, 1961, Dr. Bernice Eddy, Chief, Section on Experimental Virology, reported the induction of tumors in newborn hamsters by injection of rhesus monkey kidney cell extracts. (Proceedings of the Society of Experimental Biology and Medicine.) In her initial work, she was not able to cultivate a virus in the culture cells, nor did she observe any changes indicative of a virus when extracts of a tumor were inoculated with mouse embryo.

In further investigation, however, Dr. Eddy discovered that when the hamster tumor tissue was treated with an enzyme, the cells grew out in such a way that the fluid from the tissue culture induced tumors in hamsters. Moreover, the same fluid, when added to African green (*cercopithecus*) monkey kidney cell cultures, gave rise to degenerative changes such as those caused by SV-40.

Dr. Eddy also found the properties of the tumor-inducing substance to be essentially the same as those reported for SV-40 in 1960 by Sweet and Hilleman, i.e., the ability to pass through filters; resistance to diethyl ether; relative resistance to heat; stability on storage at -70°C ; failure to show hemagglutination of guinea pig erythrocytes; and failure to cause illness or death when injected into newborn mice.

The most significant correlation of the two agents was the recovery of SV-40 from kidney cell culture extracts that induced tumors in hamsters and, conversely, the failure to demonstrate the presence of SV-40 in extracts that did not induce tumors in hamsters. Dr. Eddy's findings, reported in Virology, have been substantiated by other investigators.

BRAIN TUMORS PRODUCED IN NEWBORN HAMSTERS BY SIMIAN VIRUS 40

The first occurrence of gliomas (tumors of the brain) following intracerebral inoculation of a virus, has been reported by Drs. Ruth Kirschstein and Paul Garber, Laboratory of Viral Immunology. The tumors, produced in newborn Syrian hamsters, occurred in the ependyma—the lining of the brain ventricles. This work followed earlier work by Dr. Kirschstein, DBS, and Dr. Allan S. Rabson, NCI, on the marked susceptibility of newborn hamsters to the induction of tumors following intracerebral inoculation of polyoma virus.

Previously, Dr. Bernice Eddy and her associates, DBS, had found that extracts of rhesus monkey kidney cell cultures produced subcutaneous sarcomas when inoculated into newborn hamsters, and that similar subcutaneous sarcomas in hamsters can be induced by inoculation of a preparation containing SV-40.

In this study, reported in *Nature*, large doses of SV-40 strain 777 were injected into the right cerebral hemisphere of each newborn hamster of a single litter; another litter served as control. On the 100th day, two of the virus-inoculated hamsters became weak and lethargic. This condition rapidly progressed to complete paralysis of all limbs. A third hamster developed similar paralysis 11 days later. Examination revealed brain tumors in the three paralyzed hamsters and in one apparently healthy hamster. In each animal the tumor filled the lateral cerebral ventricles of the brain. The tumors were classified histologically as ependymomas—true gliomas of the brain.

TYPE 3 ORAL POLIO VACCINE MEETS REQUIREMENTS FOR LICENSING

The licensing of type 3 live oral polio vaccine in March of this year made available to physicians and health officers a choice of two methods of immunization against polio—the killed inactivated (Salk) vaccine and the live attenuated vaccine prepared from Sabin strains.

Types 1 and 2 of the live vaccine were licensed in the fall of 1961. The delay in the licensing of the type 3 strain—genetically the most labile of the three—was caused by difficulties encountered under manufacturing conditions in producing five consecutive lots of vaccine which would meet the requirements for a low degree of neurovirulence in monkeys and other essential characterizations in tissue culture.

The monkey neurovirulence tests required for all three types of live polio-virus vaccines involved exhaustive studies by DBS scientists over a 2-year period. The tests comprised the intraspinal and intrathalamic injection of monkeys with dilutions of the virus strain, and the comparison of the results with those obtained in similar groups of monkeys with dilutions of the reference virus preparation made from the Sabin type 1 strain.

Evidence of the degree of neurovirulence for the three strains is determined by the number of animals at each dilution showing pathological changes in the brain and spinal cord. The monkeys are observed for paralysis during a 17- to 21-day period. No lot of vaccine is approved unless its neurovirulence is as low as that shown by the monkeys inoculated with the reference material. Since January, when the manufacturers first submitted live, oral poliomyelitis vaccine for testing, more than 150 tests have been made involving more than 4,000 monkeys. This has provided a body of information and experience that is invaluable in judging the validity of individual tests.

The genetic in vitro tissue culture marker tests have also been intensively studied to the point at which confidence in methodology and reproducibility of the tests were assured. These genetic markers are inherent characteristics of a virus strain and if the markers of an individual lot of vaccine differ from those of the seed, that lot cannot be approved for use. One such characteristic, called the temperature (t) marker, involves a demonstration of the suppression of the growth of the virus at higher temperatures, such as 40° C., as compared with growth of attenuated strains at the optimal growth temperature of approximately 36° C. Virulent virus strains, on the other hand, generally grow well at the higher temperature. While this t-marker does not effect complete correlation with virulence, it does serve to discriminate between different strains. In addition, a number of other characteristics, such as the so-called "d" and "MS" markers have been examined.

The Division also has been concerned with the development of satisfactory methods for determining virus titer (the measurement of the amount of virus in the vaccine which constitutes the potency test), and the examination of all lots for the presence of extraneous agents, such as SV-40.

FURTHER EVIDENCE OF ANTIVIRAL ACTIVITY IN MOLLUSKS

Extending their previous observations on the presence of antimicrobial factors in mollusks, Dr. C. P. Li and coworkers have demonstrated that oyster material as well as abalone material contain both antibacterial and antiviral substances. Antiviral activity against influenza virus and polio virus, as well as antibacterial activity against *Streptococcus pyogenes*, was demonstrated in oyster material in vitro and in vivo. (This work was presented at the meeting of the New York Academy of Sciences, Section of Microbiology.) Previous work by the author had shown that tissue fluid from the abalone contains antimicrobial factors which inhibit *Staphylococcus aureus* and have a protective effect against experimental poliomyelitis in mice.

Evidence of antiviral activity was demonstrated by the effect of oyster material on infection of mice and tissue cultures with influenza and poliovirus. Monkey kidney tissue cultures were treated with oyster material and infected with the three types of poliovirus. Although the reduction of cytopathic effect was only moderate, inhibition of 90 to 99.9 percent of viral growth was observed. Moreover, the incidence of paralysis in inoculated mice was reduced for each type of poliovirus by approximately 20 percent. In mice infected intranasally with influenza B virus, Great Lakes strain, the death rate was 60 to 70 percent in the untreated mice but only 20 to 50 percent in mice treated with oyster material.

The antibacterial activity of oyster material in mice infected with *S. pyogenes* was demonstrated by a 22 to 25 percent decrease in the death rate; similar results were obtained in earlier experiments with abalone tissue fluid. Since agents inhibiting poliovirus are of rare occurrence, and those which have been previously reported have not, for various reasons, been used for the treatment of diseases in man, the investigators suggest that their observations concerning antimicrobial agents in mollusks are of sufficient interest to warrant further study.

STABILITY OF TYPE 1 LIVE POLIOVIRUS VACCINE STRAIN STUDIED

Previous studies have shown an apparent random instability for all the genetic characteristics of polioviruses. Because of the importance of type 1 poliovirus infection in the epidemiology of poliomyelitis, a study was undertaken by Drs. Friedman, Kirschstein, and Borman, Laboratory of Viral Immunology, and Dr. Frederick Robbins, Western Reserve School of Medicine, to evaluate the stability of the Sabin type 1 poliovirus after gastrointestinal passage in newborn infants. (American Journal of Hygiene.)

The investigators inoculated stool material from infants into the central nervous system (CNS) of monkeys. Since alterations in the characteristics of poliovirus strains have been noted even after a single tissue culture passage, only stool material which had not been passed in tissue culture was used. The intraspinal route was selected because even as few as 10 tissue culture infectious units (TCID₅₀) of a virulent strain of poliovirus, when inoculated by this route, can cause CNS lesions or even severe paralysis in monkeys, whereas 250 to 2,500 TCID₅₀ of Sabin type 1 vaccine strains when inoculated intraspinally rarely cause histologic changes. Virus samples of low titer could thus be graded with respect to simian neurovirulence and compared to the Sabin vaccine strain which had been fed or to a known virulent type 1 strain, e.g., the Mahoney strain.

The Sabin type 1 vaccine was compared with excreted virus on the basis of its ability to multiply in cell cultures at elevated temperatures (rct/40 marker) and of its neurovirulence for monkeys. It was found that the simian neurovirulence characteristic of the vaccine tended to increase after human gastrointestinal passage in four out of six infants studied. The increase was not correlated with the duration of gastrointestinal infection by the vaccine virus, but occurred at any time after its administration. Correlation between the rct/40 marker and the simian neurovirulence characteristic of the viruses isolated from stool samples was poor.

In evaluating their findings, the authors emphasize that there is some evidence that a direct relationship between simian and human neurovirulence for poliovirus does not exist. Moreover, it has been shown in previous studies (Fox, Robbins, et al.) that vaccine viruses spread less readily in a community than do the wild strains—a fact which has a direct bearing on this problem since, in order to cause disease, a virus must spread. Thus the authors express caution concerning extrapolation from the laboratory characteristics of a virus to conclusions about its behavior in man.

THREE POLIOVIRUS TYPES RELATED ANTIGENICALLY

A study on the heterotypic responses to poliovirus in rabbits has shown that inoculation with a single poliovirus type produces neutralization capacity for the same type (homotypic) and different types (heterotypic) of polioviruses and for Echo 12 virus. The neutralizing capacity for heterotypic and heterologous viruses was shown to have properties of antibody: it was produced by antigenic stimulus, was demonstrated in heat-inactivated sera, and was not dependent upon the cellular component of the antigen. This work, reported in the *Journal of Immunology*, was carried out by Drs. Eugene V. Barnett and Samuel Baron, Laboratory of Viral Immunology.

High antibody levels for the homotypic virus, measurable in the conventional metabolic inhibition test, were produced in the rabbits 72 hours after primary inoculation with either type 1, 2, or 3 poliovirus. Using more sensitive techniques capable of detecting the homotypic responses 24 to 48 hours after inoculation, the investigators found unexpected early production of low levels of neutralizing capacity for the heterotypic polioviruses in approximately 50 percent of the inoculated rabbits. The heterotypic response was usually detectable somewhat later than the homotypic response.

Further evidence for the antigenic relationship of the three poliovirus types was demonstrated when rabbits previously immunized with type 2 poliovirus were found to have an enhanced response to the poliovirus types 1 and 3 components of trivalent vaccine as compared with the control, unsensitized rabbits.

Antibody relationships among the enteroviruses (including poliovirus) have been previously suggested and there is evidence of some protection against paralytic poliomyelitis on the basis of shared antigen by the other poliovirus types. The investigators suggest that it may be of interest to know whether similar cross protection against polioviruses occurs in man following natural infection with other enteroviruses.

DETECTION OF PPLO CELL CULTURE CONTAMINATION

A method for detecting pleuropneumonia-like organisms (PPLO) in cell cultures by the fluorescent antibody technique has been developed by Dr. Michael F. Barile, Laboratory of Bacterial Products. In his study, reported in the *Journal of Bacteriology*, Dr. Barile produced specific tissue culture PPLO antiserum using a complete rabbit system.

PPLO antigen, prepared in primary rabbit kidney cell cultures which, by cultural methods, were known to be free of PPLO, was grown on media containing rabbit serum. Antiserum prepared in the same rabbit species was adsorbed with both rabbit tissue powders and primary rabbit cell cultures and tested for freedom from media-component antibodies by agar gel diffusion procedures before conjugating it with fluorescein.

One hundred and two tissue cell cultures from 17 separate laboratories were examined for PPLO by both fluorescent antibody and cultural procedures. PPLO was isolated from 48 of the tissue cell cultures that were found to be PPLO-positive by the fluorescent antibody procedure, and results of the two procedures agreed in 101 of the 102 cultures. None of the 10 primary cell cultures examined were contaminated with PPLO, whereas 48 of the 92 continuous cell cultures were. Of the 64 continuous cell cultures grown in media containing antibiotics, 48 were contaminated, whereas only 2 of 28 cell cultures grown on antibiotic-free media were similarly contaminated.

These findings support the view that PPLO contamination of cell cultures is probably due to bacterial contaminants which revert to L-forms (filterable variants of a particular bacterium). Of the cell cultures contaminated with PPLO, 46 of 48 were grown in media containing antibiotics, principally penicillin, an agent well-documented for inducing L-formation of bacteria.

POLIOVIRUS TAGGED BY PHOTOSENSITIZATION

A method of differential inactivation of parent virus, leaving intact only progeny virus in a culture harvest or, conversely, only the parent virus and destroying all the progeny, has been developed by Dr. C. W. Hiatt, Laboratory of Biophysics and Biochemistry.

The incorporation of proflavine, an organic dye, into the ribonucleic acid of poliovirus during intracellular maturation, was reported in 1960 by Schaffer. It has subsequently been found that the virus produced in the presence of this dye is readily inactivated on exposure to light. The DBS workers have utilized this photosensitivity as a phenotypic tagging device for experiments in which it is desirable to distinguish between new virus and cell-associated virus persisting from the inoculum.

Monolayer cultures of trypsinized rhesus monkey kidney cells in medium 199 containing 0.2 milligram percent proflavine are inoculated at 36° C. in total darkness. Normal yields of poliovirus are obtained, but the virus so produced is very sensitive to light. The fraction surviving 5 minutes exposure to polychromatic visible light (1 watt per square centimeter) is less than 10^{-5} . However, the offspring of the photosensitized virus, being normal, are not affected. Thus it is possible to detect even one new virus particle in the presence of more than 1,000 particles of the parent generation.

This differential inactivation procedure is useful not only in the study of the dynamics of virus replication in various cell systems, but because it may also offer a means of selecting mutants with desirable characteristics. For example, to date, only primate tissue culture cells have been used for the cultivation of poliovirus. Adaptation of poliovirus to nonprimate cell cultures would offer the distinct advantage of avoiding the problem of adventitious agents of monkey origin. But if poliovirus mutants capable of multiplying in nonprimate systems occur, their detection may be very difficult. In the system devised, all the parent virus can be destroyed, and the infectious particles remaining—being of the new generation—may include mutants which can be adapted to grow in cell cultures that are advantageous for vaccine production.

INFECTION OF HUMAN CARCINOMA AND PRIMARY CHICK EMBRYO CELLS WITH SV-40

Multiplication of SV-40 in two continuous lines of malignant cells of human origin—HeLa cells for approximately 8 months and HEP-2 cells for 6 months—has been demonstrated by Dr. Bernice Eddy, Chief, Section on Experimental Virology (Proceedings of the Society of Experimental Biological Medicine).

Infection of the HeLa cells, and to a lesser extent the HEP-2 cells, was accompanied by changes in the appearance of the cultures depending on the concentration of SV-40 in the inocula. SV-40 was found to multiply in each of the cell lines under study and the cells continued to shed virus into the fluid during periods of observation ranging from 178 to 241 days. These results confirm the observation of Shein, Enders, and Koprowski that the virus is capable of growing in human cells.

The concentration of SV-40 in the two human cell lines was high. The titer of the HeLa cell fluids varied from $10^{-8.5}$ to $10^{-9.5}$, and fluid from the HEp-2 cells reached $10^{-6.0}$.

Newborn hamsters injected with fluid from two HeLa cultures, one incubated for 94 days and the other for 77 days, developed subcutaneous tumors that were typical of those induced by SV-40.

SV-40 was also shed into the nutrient fluid of chick embryo cultures but the titers, as determined in cercopithecus monkey kidney cells, were low and hamsters injected with the fluid failed to develop tumors within a 160-day period.

TEST FOR HEMOLYTIC ACTIVITY OF EL TOR CHOLERA VIBRIO

A reproducible test for the detection of the hemolytic activity of the El Tor vibrio has been developed by Dr. John C. Feeley, Laboratory of Bacterial Products (Bulletin for World Health Organization). This activity, identifiable by the disruption of the red cells of sheep or goat blood following incubation in a broth culture of vibrios, is the principal characteristic which distinguishes the El Tor from the classic cholera vibrio.

Although many vibrios possess hemolytic properties, the El Tor designation is applied only to those strains agglutinable in cholera O group I serum. These strains have only rarely been associated with clinical cholera in Egypt and India, the geographic areas in which they were most frequently isolated.

Hence they came to be regarded as nonpathogenic. However, in the 1930's and succeeding years, cholera caused by hemolytic vibrios occurred in Indonesia. In 1960, the incidence of El Tor infection increased markedly in southeast Asia, and in September 1961, a major outbreak occurred in the Philippines. Dr. Feeley participated in diagnosing the Philippine epidemic and brought back cultures of the vibrio for further study. Inconsistencies in existing tests for differentiation of hemolytic from nonhemolytic vibrios prompted him to make a detailed study of the hemolysin production of El Tor.

Using seven different commercial dehydrated media for culture broths, he found that detection of the hemolytic property of El Tor was profoundly affected by the nature of the medium and the duration of incubation time of the culture.

In an alkaline medium, the hemolysin produced by most cultures disappeared within 24 hours; in an acid medium, maximum hemolysin production was observed at 48 hours; in a balanced acid-alkaline medium, maximum hemolysin production occurred consistently at 24 hours.

Although differentiation of El Tor from classic cholera vibrios is no longer significant in terms of international quarantine, since, in 1962, the World Health Organization ruled that El Tor infections should be included under the definition of cholera, the test is of value in the bacteriological characterization of cultures.

ROLE OF LEUKOAGGLUTININS LIMITED IN TRANSFUSION REACTIONS, STUDY SHOWS

Persons whose blood contains leukoagglutinins—substances that cause the white blood cells to clump together—are no more likely to develop febrile (fever) reactions to blood transfusions than are those whose blood lack these substances. This finding was reported by Dr. Sherwin V. Kevy, Laboratory of Blood and Blood Products, following a 4-month study of NIH Clinical Center patients.

Previous studies by other investigators had indicated that both leukoagglutinins and clinical reactions to transfusion are more frequent in multi-transfused patients. Reactions due to leukoagglutinins have also been documented. Thus it has been inferred that the presence of leukoagglutinins denotes a causal relationship between donor leukocytes (white blood cells) and transfusion reactions. This study indicates that this is not necessarily true. In 185 patients who were tested and then transfused without regard to leukocyte compatibility, the incidence of reactions in the patients with leukoagglutinins was no more than for patients without leukoagglutinins, despite the fact that the former had more exposures (10.9 units of blood per patient) than the latter (6.1 units per patient).

This study was part of a detailed survey of patient response to transfusion, involving more than 10,000 transfusions given over a 4-year period to more than 1,500 patients; 276 febrile reactions, none of which was hemolytic, oc-

curred in 118 of the patients; 18 percent responding with fever to transfusion did so following their first transfusion. Many patients had only one transfusion reaction, despite many further transfusions, and others had successive reactions followed by numerous reaction-free transfusions of blood from which leukocytes had not been removed.

In view of these findings, the investigators assess as unwarranted any attempt to reduce the incidence of transfusion reactions by routinely supplying leukocyte-poor blood to patients who have multiple transfusion reactions and leukoagglutinins. They warn that if the cause of such reactions is automatically assigned to leukocyte incompatibility, it might preclude the study of other possible causes of febrile, nonhemolytic transfusion reactions.

A complete report of this study has been published in *Transfusion*.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

TUESDAY, MARCH 12, 1963.

WITNESSES

DR. ROBERT A. ALDRICH, DIRECTOR, NATIONAL INSTITUTE OF
CHILD HEALTH AND HUMAN DEVELOPMENT

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF
HEALTH

DR. DONALD HARTING, ASSISTANT DIRECTOR, NATIONAL INSTITUTE OF
CHILD HEALTH AND HUMAN DEVELOPMENT

GERALD ATCHISON, BUDGET OFFICER, NATIONAL INSTITUTE OF
CHILD HEALTH AND HUMAN DEVELOPMENT

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL
INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

PERSONAL BACKGROUND OF DIRECTOR

Mr. FOGARTY. The committee will come to order.

We have before us this afternoon the justifications for the new Institute of Child Health and Human Development.

Dr. Aldrich, this is your first appearance before our committee. For the benefit of the committee, would you give us some of your background? This is the usual question I ask of those who appear before this committee for the first time.

Dr. ALDRICH. Mr. Chairman, I am a native of Winnetka, Ill., and took my undergraduate degree at Amherst College. I graduated from Northwestern University Medical School and following service in World War II overseas I received my graduate training in pediatrics at the University of Minnesota.

Following that, I spent 2 years on the staff of the Mayo Clinic in pediatrics and from there I went to the University of Oregon Medical School, Portland, in full-time teaching and research with appointments in the departments of Pediatrics and Biochemistry. In 1956 I became chairman of the Department of Pediatrics at the University of Washington in Seattle, which post I held until March 1 of this year.

My field of clinical training is entirely in child health and development and pediatrics. My research activities have been almost entirely devoted to the biochemistry of inborn chemical disorders.

I have worked intensively in the field of porphyrin pigment metabolism and with the related bile pigments. One of the bile pigments, bilirubin, is a noxious agent for the brain of newborn infants and can cause extensive central nervous damage with resultant mental retardation. This research interest in injurious effects of chemicals on the newborn or fetus has increased in recent years.

I am also interested secondarily in human behavior in our culture, but that is not my major research interest.

GENERAL STATEMENT

Mr. FOGARTY. Thank you, Doctor. You have a statement for the committee now?

Dr. ALDRICH. I have a rather extensive statement.

Mr. FOGARTY. We will place that in the record and you may summarize it.

(The statement follows:)

Mr. Chairman and members of the committee, at this time it is my pleasure and privilege to appear before you on behalf of the newly created Institute of Child Health and Human Development.

The legislation (H.R. 8398), which authorized the Surgeon General to establish this new Institute represents a dynamic contribution to the well-being of our present and future society. The President and Congress can take great pride in having recognized that an urgent need of our Nation was to create a program devoted to the stimulation and development of research into the nature of human development and the health problems of children and mothers. A greater focusing on the studies of the continuing processes of growth and development that characterize all biological life—from reproduction and prenatal development through infancy and childhood and into the stages of maturation and senescence—will be a major factor in closing the gap between our aspiration and accomplishments.

The passage of this legislation provided the means to achieve a better understanding of the fundamental process of aging and the factors which influence an individual's growth and development during his formative years. The National Institute of Child Health and Human Development will provide the means to foster in a very positive way the opportunity for investigators from a variety of scientific disciplines in our universities and research centers to come together and systematically investigate the nature of human development and the problems of child health. The sciences which underlie such studies of development are represented in medical, biological, and behavioral and social sciences. In conception, this Institute will require the techniques and theories of many scientific disciplines in an effort to understand the basic life processes, and the biology of reproduction, development, differentiation, and senescence of human beings as a species. This is a more difficult task in some ways than the study of a single disease or a particular organ system. The National Institute of Child Health and Human Development will stimulate and provide assistance to investigators from universities and other institutions of higher learning who wish to study such problems as congenital malformations, mental retardation, or prematurity on the one hand, and the difficulties of the aging and the aged on the other. This Institute will utilize all of the available mechanisms to advance science which have been utilized by the categorical institutes in such an excellent fashion. Unique ways of advancing science in these important areas will emerge from this new Institute.

PROGRAM PLANS AND DEVELOPMENTS IN FISCAL YEAR 1963

One of the organizational program developments to date has been the determination of staffing requirements for this organization. In addition, we are now identifying programs within the categorical institutes, which are more re-

lated to the achievement of a better understanding of human development than to their categorical missions. The volume of activity now supported by these institutes, with relevance to NICHD, would exceed the administrative capacity of a new organization in its early stages of development. Accordingly, the transfer of functions has been planned in such a way as to accomplish the following objectives:

1. Our first objective, in the initial year, is to provide for the transfer of a broad base of relatively small research and training activities now distributed throughout all of the categorical programs. This should permit the development of administrative machinery to administer effectively a modest-size program of extramural research and training grants and to maintain appropriate and continuing relationships with the other institutes and divisions. This should also permit initial grouping of the most relevant project-grant support into four major research program areas, giving them a more meaningful focus.

The first research area involves problems relating to human reproduction and fetal development. Research of this kind is now supported by the other institutes. Criteria are now being established to allow for a more clear-cut assignment of support responsibilities to the respective institutes. As the program of the NICHD is progressively implemented, there will be less overlap of responsibility for support in research areas of mutual interest. Examples of the kinds of criteria which may be used are the following: NICHD will support studies of reproductive physiology, embryogenesis, gestation, placental and uterine physiology, and the growth, development and physiology of the reproductive organs. However, NICHD will not support studies which are primarily to add to the knowledge of a basic science such as biophysics, anatomy, genetics, biochemistry, or physiology. Also, studies directed toward advancement of a scientific discipline *per se*, would remain with NIGMS.

The separation of interests between NCI and NICHD follows similar lines of logic. Cell-differentiation studies involving reproductive, embryonic, or fetal cells will be supported by NICHD; whereas cell differentiation studies of mature or malignant cells may be supported by NCI.

Our second research area includes factors involving the birth process, adaptation of the newborn to an external environment, and problems of the mother and newborn. Here, support will be given to studies on the initiation of labor, obstetrical delivery, perinatal care, prematurity, respiratory distress of the newborn, physiologic adaptation of the newborn infant, obstetrical problems in the mother attendant upon birth, toxemia of pregnancy, lactation, maternal and infant behavioral relationships.

The third major research area deals with normal human growth and development and special child health problems. Foremost, the study of normal aspects of human growth and development will be encouraged by this Institute. Included in this will be studies on the growth and differentiation of the infant and child; maternal and paternal factors affecting child growth and development; factors causing abnormal development such as mental retardation, congenital malformations, inborn errors of metabolism; normal development of physiologic systems; intellectual development; nutrition and body composition; and the process of maturation.

An example of criteria for assignment in this area might be that studies of intellectual development, and of the determinants, including maternal attitudes, which produce both intellectual deficit and intellectual excellent will be supported by NICHD. The disorders of mental health affecting intellectual function, such as schizophrenia, will be supported by the NIMH.

The final research area will support the investigation of the Root processes of aging in early life. Primary emphasis will be placed on the basic biological, behavioral, and medical aspects of aging. This will include studies on the endocrinology and nutrition of the infant and child as it relates to the aging process; on enzymatic and other biochemical changes in animals as they relate to aging; on progeria, which is a unique "experiment of nature" and illustrates nearly all aspects of the aging process; and on physical and environmental factors which may be correlated with the aging process.

2. Our second objective in the initial year is to develop the administrative structure and method of support for a limited number of new activities which will become operational programs in 1964. These programs will be discussed later in this statement.

3. Our third objective is to provide and carry out the necessary systematic and extensive review of the broadly planned and organizationally complex programs such as the multidisciplinary research program-projects, the perinatal

collaborative study, and the Children's Clinical Research Centers. Such a detailed review is necessary before a decision can be made on transfer of programs between institutes or before a new administration base could be established.

PROGRAM PLANS FOR 1964

In our program plans for fiscal year 1964, we propose to establish a number of specialized information centers within the Institute designed to provide focal points for informational and consultant services related to research in maternal health, child health, mental retardation, and the field of aging. In each of these areas, there is an evident need for a centralized national point of contact for the reference and guidance of both the lay public and scientific investigators.

In another major activity, the professional staff of the Institute will utilize scientific consultants to identify neglected areas of research. This will be accomplished by extensive review of specialized problem areas and, on this basis, they will recommend future program development. Consultants will participate, as individuals or as selected groups, in conference with appropriate Institute staff members on specific problem areas. Highlighting these conferences will be the establishment of a series of meetings with scientists and professional experts in the field of mental retardation. The proceedings of these conferences will be published so that scientific personnel and other interested individuals may be kept abreast of the status of scientific knowledge in these areas. International representation at these meetings will afford the opportunity to draw upon recognized competence in these fields from all countries.

During fiscal year 1964 there would be several specific program areas which would be expanded. Receiving foremost attention would be research training. The support of research training in developmental biology (including both pre- and post-doctoral programs) would be enlarged. This is a basic field for the execution of research in human development, and as pointed out by the President's Panel on Mental Retardation, it is a crucial field for research in mental retardation. It is also planned to enlarge the post-doctoral research training in obstetrics, pediatrics, behavioral development, and teratology, with emphasis on fundamental investigations. Cross-disciplinary research training, such as pediatric training for neurologists, behavioral science training for pediatricians, etc., to deal with the special childhood problems (i.e., congenital disorders, prematurity, mental retardation) will be encouraged. Serious consideration is being given to the stimulation of new academic departments devoted to research and research training in gerontology through the provision of substantive grant support.

In the research grant area, high priority would be given to the support of research in these following four programs:

First, a program of research relating to premature labor and the development of premature infants. Although it is an important area in itself as the leading cause of neonatal death and costing the Nation an estimated \$300 million annually for medical and hospital care, this is a problem that is also intimately related to the occurrence of mental retardation.

Second, a program on the biological and behavioral factors associated with the mentally retarded.

Third, a research program correlating the interrelationships between the maternal environment, physical environment, the placenta, and the fetus.

Fourth, a research program in developmental pharmacology. It is necessary that we increase our knowledge of the differential effects of various pharmacologic agents at various stages of embryologic development, during childhood, pregnancy, and the aging years.

Finally, in 1964, the NICHD will initiate the development, in conjunction with outstanding universities, of a small number of major centers for research and research training in human development. Initially, these centers will provide a focus for the broadly based research and training activities involving a number of scientific disciplines. Emphasis will be on developmental abnormalities that result in mental retardation and on perinatal biology.

SUMMARY

During 1963, NICHD will concentrate on bringing together diverse research activities to provide a greater research contribution to important problem areas of child health and human development. Research projects primarily focused on the main objectives of the categorical institutes will remain within those

institutes even though they may relate to child health. Major well-differentiated program will be reviewed for appropriations of transfer to NICHD. This will be done when it is apparent that transfer would strengthen the total effectiveness of the NIH effort.

In 1964, our plans would permit major emphasis to be given to research training of pediatricians, obstetricians, and those interested in research careers in various aspects of child development, reproduction, and the aging process. We propose the establishment of a small number of major centers for research in human development which would be initiated in 1964 and extended in 1965. These centers would initially be focused on problems of mental retardation and perinatal biology. In the area of research grants, encouragement would be given to research on prematurity, mental retardation, prenatal influences, developmental pharmacology, and aging.

For these activities which I have outlined, Mr. Chairman, we propose a budget of \$34 million which would be derived by a transfer from the other appropriations of the National Institutes of Health.

AUTHORIZATION OF INSTITUTE

Dr. ALDRICH. Mr. Chairman and members of the committee, at this time it is my pleasure and privilege to appear before you on behalf of the newly created Institute of Child Health and Human Development.

The legislation (H.R. 8398) which authorized the Surgeon General to establish this new Institute represents a dynamic contribution to the well-being of our present and future society. The President and Congress can take great pride in having recognized that an urgent need of our Nation was to create a program devoted to the stimulation and development of research into the nature of human development and the health problems of children and mothers. A greater focusing on the studies of the continuing processes of growth and development that characterize all biological life—from reproduction and prenatal development through infancy and childhood and into the stages of maturation and senescence—will be a major factor in closing the gap between our aspirations and accomplishments.

During 1963, the National Institute of Child Health and Human Development will concentrate on bringing together diverse research activities to provide a greater research contribution to important problem areas of child health and human development. Research projects primarily focused on the main objectives of the categorical institutes will remain within those institutes even though they may relate to child health. Major well-differentiated programs will be reviewed for appropriateness of transfer to the National Institute of Child Health and Human Development. This will be done when it is apparent that transfer would strengthen the total effectiveness of the National Institutes of Health effort.

PLANS FOR 1964

In 1964, our plans would permit major emphasis to be given to research training of pediatricians, obstetricians, and those interested in research careers in various aspects of child development, reproduction, and the aging process. We propose the establishment of a small number of major centers for research in human development which would be initiated in 1964 and extended in 1965. These centers would initially be focused on problems of mental retardation and perinatal biology. In the area of research grants, encouragement would be given to research on prematurity, mental retardation, prenatal influences, developmental pharmacology, and aging.

For these activities which I have outlined, Mr. Chairman, we propose a budget of \$34 million which would be derived by a transfer from the other appropriations of the National Institutes of Health.

DELAY IN GETTING JUSTIFICATIONS TO THE COMMITTEE

Mr. FOGARTY. Thank you, Doctor.

When did you get the justifications to the committee? This is not the first time I have asked this question since we started hearings with the Department of Health, Education, and Welfare. We have had more trouble with the justifications this year than ever before, and they were rather late last year.

Dr. SHANNON. They were submitted 2 weeks ago to our budget officer.

Mr. FOGARTY. When did they arrive at the committee? That is what counts with us.

Mr. KELLY. There is a note on mine, Mr. Chairman, which would indicate that we submitted it to the committee on the 1st of March, which was subsequent to the date on which we had submitted the other PHS justifications.

Mr. FOGARTY. The note that I have is the 5th of March, last Tuesday.

Dr. SHANNON. Mr. Chairman, the submission is the responsibility of the National Institutes of Health. We have been loath to proceed without the special advice of Dr. Aldrich, who actually came on full-time duty March 1 of this year.

During the past 3 months, he has been spending approximately 7 or 8 days a month defining the program with us. He has had a very heavy burden at the University of Washington. This type of transitional administrative setup has led to delays in the preparation of formal justifications.

Mr. FOGARTY. When was the legislation authorizing this institute enacted?

Dr. SHANNON. October of 1962.

We could have submitted the justification earlier, but we felt it would be sounder if it were possible to delay the actual submission of the opening statement to this committee, until Dr. Aldrich's arrival, because in a very real sense, his opening statement commits this new Institute to specified broad program areas for the coming year. It may well be, sir, that we took an undue liberty but we thought it would be better if we could wait until such time as we could obtain such a statement from Dr. Aldrich.

We are very sorry, sir, but this is the cause of the delay.

TRANSFERS IN FROM OTHER APPROPRIATIONS

Mr. FOGARTY. These justifications show funds being transferred in, from other accounts, but I do not find any comparable transfer out in the other institutes' justifications. Why is that?

Dr. SHANNON. These transfers "in" are really authorizations for transfers to this program. The specific dollar value of the funds to be transferred will be subject to negotiation between Dr. Aldrich's Institute and the institutes concerned. I have a more detailed breakdown of the proposed transfers shown by activity, which I will be glad to make available for the record. This represents a stage beyond the budget discussions with the individual institutes.

(The information referred to follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
Source of funds 1964
 [In thousands]

	NIGMS	NCI	NIMH	NHI	NIDR	NIAMD	NIAID	NINDB	NICHD, total
Grants:									
Research.....	\$3,500	\$840	\$7,117	\$3,535	\$998	\$2,782	\$1,838	\$2,590	\$23,200
Fellowships.....	1,250	534	507	166	88	60	90	105	2,800
Training.....	2,600	270	1,525	420	150	1,800	230	305	6,800
Subtotal grants.....	7,350	1,644	9,149	4,121	1,236	4,142	2,158	3,000	32,800
Direct operations:									
Collaborative studies.....			400						400
Review and approval:									
Direct funds.....	224	5	50	20		20	10	15	344
Reimbursement to management fund.....	76								76
Subtotal.....	300	5	50	20		20	10	15	420
Program direction:									
Direct funds.....	358								358
Reimbursement to management fund.....	22								22
Subtotal.....	380								380
Total transfer.....	8,030	1,649	9,599	4,141	1,236	4,162	2,168	3,015	34,000

JUSTIFICATION OF THE ESTIMATE

Mr. FOGARTY. Doctor, you are starting off under sort of adverse conditions, just getting on the job the first of March and everything being in a state of flux but still having to come before a congressional committee and justify the expenditure of \$34 million, with only 10 pages of justifications. We will put the justifications in the record. (The material follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Amounts available for obligation, 1964

Transfer from other accounts (total obligations)----- \$34,000,000

Obligations by activities

Description	1964 estimate	
	Position	Amount
Grants:		
Research.....		\$23,200,000
Fellowships.....		2,800,000
Training.....		6,800,000
Direct operations:		
Collaborative studies.....	40	400,000
Review and approval of grants.....	39	420,000
Program direction.....	38	380,000
Total obligations.....	117	34,000,000

Obligations by objects

1964 estimate

Total number of permanent positions.....	117
Full-time equivalent of other positions.....	2
Average number of all employees.....	90
Number of employees at end of year.....	110
11 Personnel compensation:	
Permanent positions.....	\$718,000
Positions other than permanent.....	16,000
Other personnel compensation.....	8,000
Total personnel compensation.....	742,000
12 Personnel benefits.....	71,000
21 Travel and transportation of persons.....	100,000
22 Transportation of things.....	4,000
23 Rent, communications, and utilities.....	35,000
24 Printing and reproduction.....	25,000
25 Other services.....	56,000
Payment to "National Institutes of Health management fund".....	98,000
26 Supplies and materials.....	40,000
31 Equipment.....	31,000
41 Grants, subsidies, and contributions.....	32,800,000
Subtotal.....	34,002,000
Deduct quarters and subsistence charges.....	-2,000
Total obligations.....	34,000,000

Source of funds

<i>Activity</i>	<i>Amount</i>
National Institute of General Medical Sciences-----	\$8, 030, 000
National Cancer Institute-----	1, 649, 000
National Institute of Mental Health-----	9, 599, 000
National Heart Institute-----	4, 141, 000
National Institute of Dental Research-----	1, 236, 000
National Institute of Arthritis and Metabolic Diseases-----	4, 162, 000
National Institute of Allergy and Infectious Diseases-----	2, 168, 000
National Institute of Neurological Diseases and Blindness-----	3, 015, 000
Total-----	34, 000, 000

INTRODUCTION

During the 87th Congress, legislation was enacted by the Congress which authorized the Surgeon General to establish the National Institute of Child Health and Human Development. The initial organization of this new Institute is composed of transferred functions or units—such as the centers for research in aging and in child health heretofore located within the National Institute of General Medical Sciences. Major program components of the new Institute will be established from programs transferred from other Institutes. Essentially, the establishment of this Institute represents a major step toward the more purposeful focusing of selected research and training activities in an effort to provide fundamental new understanding of the developmental processes through all stages of life and to stimulate new interest and effort in these important areas.

Major attention will be focused on the study of the continuing process of growth and development that characterizes all biological life—from reproduction and prenatal development through infancy and childhood and on into the stages of maturation. The new Institute will engage in the development of more effective research efforts in the following areas:

1. The biological, physiological, and behavioral aspects of human reproduction, growth, and development.
2. Studies in the prenatal and perinatal period in human development, from conception until shortly after birth.
3. Obstetrical and pediatric problems not directly related to specific disease interests of the other Institutes.
4. Studies of the process of maturation and senescence.
5. Studies in special problem areas of human development, such as mental retardation.

Preliminary analyses of present activities of the several Institutes and divisions of the National Institutes of Health, with various degrees of relevance to the broad mission of NICHD, indicate that the total volume of activity now supported would far exceed the capacity of a new organization to effectively administer and advance. Accordingly, the transfer of functions is being planned in such a way as to accomplish the following objectives:

1. To provide in 1964 for a manageable base of research and training grant activities through the transfer of program elements which are now distributed through all of the categorical programs. This should permit the opportunity to develop the administrative machinery to effectively administer a modest size program of extramural research and training grant support with appropriate and continuing staff working relationships with all of the existing Institutes and divisions. This should also permit the initial grouping of the most relevant project grant support now distributed among many programs into four major program areas which can be given more meaningful focus and greater impact. These four general areas of broad significance for national health are as follows:

- (a) Problems relating to human reproduction and fetal development.
- (b) Factors involving the birth process, adaptation to an external environment, and problems of the mother and newborn.
- (c) Normal human growth and development and special child health problems.
- (d) Identification of the root processes of aging in early life.

2. To permit initial efforts in the purposeful expansion of new activity to be focused on a small number of relatively urgent activities outlined below in 1964 program plans.

3. To allow for the systematic and extensive review that is necessary to determining the extent to which present broadly planned and highly organized programs (e.g., collaborative study of NINDB), theoretically in the purview of the new Institute, would actually benefit from transfer in a subsequent year.

PROGRAM PLANS FOR 1964

In 1964 the Institute will implement plans developed during 1963 for development of the organization and for the orderly assimilation into program components of activities to be transferred from the other Institutes. Specific program areas to be given high priority for development are summarized below.

Research grants

1964 estimate

Research projects----- \$23, 200, 000

High priority will be given to the support of research in the following problem areas:

1. Research relating to premature labor and the development of premature infants. Although an important area in itself as the leading cause of neonatal deaths, this is a problem that is also intimately related to the occurrence of mental retardation.

2. Research relating to the biological and behavioral factors involved in the abnormal development of the mentally retarded.

3. Research relating to the interrelationships of the maternal environment, the placenta, and the fetus.

4. Research in developmental pharmacology, focused on increasing knowledge of the differential effects of various pharmacologic agents at various stages of embryologic development, during childhood, in pregnancy, and during the aging years.

The Institute also proposes to award grants which would be made to outstanding universities to initiate action in the development of major centers for research and research training in human development. One or more of these centers would be primarily focused on the developmental abnormalities that result in mental retardation, and one or more would be focused on perinatal biology. These latter centers would be broadly concerned with problems in the fetus and newborn as they are related to the events that take place during pregnancy and parturition.

Training

1964 estimate

Fellowships----- \$2, 800, 000

Training----- 6, 800, 000

In 1964 the National Institute of Child Health and Human Development will assume direction of the pediatric training program presently supported through the National Institute of Arthritis and Metabolic Diseases and the developmental sciences training program presently administered by the National Institute of General Medical Sciences. The NICHD will also acquire, through transfer, support funds for selected fellowships and training grants now distributed throughout the categorical Institutes which are pertinent to the production of research competency in the areas relevant to the mission of the new Institute.

Areas to be given high priority in 1964 include the following: Continuation of research training in developmental biology (both predoctoral and postdoctoral programs) which include the broad fields of embryology; mechanisms of cellular growth; differentiation and metabolism of the developing ovum and fetus; the general field of animal reproduction; infertility; morphogenesis; placental transfer; physiology and endocrinology; biochemistry of sex hormones; enzymology and subcellular particulate metabolism as related to human development; reproductive endocrinology; uterine physiology; and maternal circulation and maternal-fetal relationships. This training in developmental biology as pointed out by the President's Panel on Mental Retardation, is a basic requirement for fruitful research on the problems of mental retardation.

We will continue to support the postdoctoral research training programs in clinical obstetrics, pediatrics, behavioral development, and teratology, with added emphasis on basic research.

Serious consideration is being given to future support of training and career opportunities in research gerontology. Cross-disciplinary research training, such as pediatric training for neurologists, behavioral science training for pediatricians, etc., to deal with the special childhood problem (i.e., congenital disorders, premature labor, mental retardation) will be encouraged.

Direct operations

	<i>1964 estimate</i>
Collaborative studies-----	\$400, 000
Review and approval-----	420, 000
Program direction-----	380, 000
Total-----	1, 200, 000

INTRODUCTION

Emphasis will be given in 1964 to the further development of the organizational structure established initially through a nucleus of staff transferred from the National Institute of General Medical Sciences. Of primary importance will be the establishment of specialized information units within the organization designed to provide focal points for informational and consultative services related to research in maternal health, child health, mental retardation, and the field of aging. In each of these areas there is an evident need for a centralized national focal point of contact for the reference and guidance of scientific investigators, members of the health professions, and the lay public.

COLLABORATIVE STUDIES

The sum of \$400,000 is requested to support information services connected with the mental retardation centers program. An information center will serve as the focal point for and the source of information regarding Government research and Government-supported research in mental retardation. Its function of making findings of ongoing and completed research available both to the scientific community and the general public is a necessary adjunct to a positive Government-supported program of research in mental retardation. Information of this nature is of benefit to researchers in planning further work in the field, and its availability lessens the possibility of duplication of research effort. In addition, support would be provided for the conduct of highly specialized conferences which would deal in depth with specific research problems underlying mental retardation. The conferences would facilitate communication among scientists in discrete fields of research, both at laboratory and clinical levels, and include subjects of concern to both the biological and the behavioral sciences.

REVIEW AND APPROVAL

This activity will support the Institute's professional and clerical staff, and the activities of our National Advisory Child Health and Human Development Council, in the review and processing of applications under the various grant programs of the Institute. The staff will be responsible for the careful evaluation and presentation of applications for Council consideration, which includes:

1. Securing of complete information about applications for research and training support.
2. Application of NIH and Institute policies affecting the grant programs.
3. Arranging for the several meetings of the Council each year.
4. The processing of applications after Council recommendation.
5. Providing analyses of progress in the scientific fields related to child health and human development.

In addition, the "Review and approval" activity will maintain appropriate relations with grantee institutions and investigators for interpretation of policies governing acceptance and utilization of grant funds and for consultation designed to improve the quality of grant preparation. This activity also maintains records on the financial aspects of active grants and initiates action to assure payments at proper time.

The "Review and approval" activity will have responsibility for formulating policies and procedures governing administrative and technical review of center and other special program grant applications, conducting this review and evaluation through committees composed of non-Government consultants. In the

review process, site visits to institutions will be necessary by a team of advisory consultants to obtain information for a comprehensive appraisal of the proposed projects for reference in conjunction with subsequent review of requests for support by the Institute.

Because frequently the Child Health and Human Development Institute will be dealing with grant requests in new and novel research areas, it is essential that the Institute's mechanisms for review and appraisal of applications be kept flexible to meet the needs of unique proposals. With the creation and implementation of new programs, the need for a trained staff equipped to handle unusual technical reviews is mandatory.

PROGRAM DIRECTION

Office of the Director

The Director of the National Institute of Child Health and Human Development is responsible for broad policy formulation and implementation and general direction essential to the coordination and conduct of intramural and extramural research and other activities of the National Institute of Child Health and Human Development. These responsibilities include close cooperation with the National Advisory Child Health and Human Development Council and continuous liaison with other parts of the Public Health Service and the Department of Health, Education, and Welfare, to assure effective program relationships and cooperative effort and exchange of information with other scientific organizations, and to coordinate research in the child health and human development area on a broad national scale.

Technical Communications Branch

They will be responsible for reporting on programs and research accomplishments, and participate in planning the collection and dissemination of child health and human development information to the medical profession and to the public.

Program Planning and Analysis Branch

Program Planning and Analysis Branch will have the responsibility for analyzing the ongoing research functions fostered by the National Institute of Child Health and Human Development and assessing the progress in the major programs. Such analysis will become increasingly important as the extramural research and the training grants programs grow in size and complexity.

Since the Institute is in its early formative stages, its present organization is a transitional one and as the Institute leadership gains more experience in actual operations and its programs grow in scope and volume, it will be necessary that we stay as flexible as possible to insure that organizational changes can be accomplished to accommodate program needs.

BUDGET REQUEST COMPARED WITH CURRENT OBLIGATIONS

Mr. FOGARTY. Now, in other justifications—and I am not blaming you because you are new to this job—but we always have figures comparing the current years obligations for each activity with what is requested for the next year, but in your justifications, I do not see any 1963 figures we can compare with the amounts requested for 1964.

Dr. SHANNON. The figures for 1963 are contained within the appropriations of the existing institutes. Precise figure for 1963 would not be very meaningful at this period of time in relationship to the proposed "Child health and human development" appropriation. I can say it is our judgment that of the \$34 million, we have estimated a maximum of \$26 million for the transfers from other institutes to Dr. Aldrich's program, and have attempted to make available an additional sum of new money for research grants, for training, and for special programs in areas such as mental retardation, as well as for program direction, and review and approval.

In this distribution our estimate is that Dr. Aldrich will have for new programs and purchases about \$8 million.

Mr. FOGARTY. Will you place in the record revised tables to show 1963 figures comparable to the 1964 figures on pages 1 and 2?

Dr. SHANNON. We will be glad to do that, sir.

(The material follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Amounts available for obligation

	Comparative 1963	1964
Appropriation.....	\$25,700,000	\$34,000,000
Transfer to "Operating expenses, PBS," GSA.....	-15,000	-----
Total.....	25,685,000	34,000,000

Obligations by activities

	Comparative 1963 estimate		1964 estimate		Increase or decrease	
	Position	Amount	Position	Amount	Position	Amount
Grants:						
Research.....		\$18,000,000		\$23,200,000		+\$5,200,000
Fellowships.....		2,000,000		2,800,000		+800,000
Training.....		5,000,000		6,800,000		+1,800,000
Direct operations:						
Collaborative studies.....			40	400,000	+40	+400,000
Review and approval of grants.....	29	315,000	39	420,000	+10	+105,000
Program direction.....	38	370,000	38	380,000	-----	+10,000
Total obligations.....	67	25,685,000	117	34,000,000	+50	+8,315,000

Obligations by object

	Comparative 1963 estimate	1964 estimate	Increase or decrease
Total number of permanent positions.....	67	117	+50
Full-time equivalent of other positions.....	2	2	0
Average number of all employees.....	51	90	+39
Number of employees at end of year.....	53	110	+57
11 Personnel compensation:			
Permanent positions.....	\$393,000	\$718,000	+\$325,000
Positions other than permanent.....	14,000	16,000	+2,000
Other personnel compensation.....	3,000	8,000	+5,000
Total personnel compensation.....	410,000	742,000	+\$332,000
12 Personnel benefits.....	39,000	71,000	+32,000
21 Travel and transportation of persons.....	40,000	100,000	+60,000
22 Transportation of things.....	3,000	4,000	+1,000
23 Rent, communications, and utilities.....	11,000	35,000	+24,000
24 Printing and reproduction.....	15,000	25,000	+10,000
25 Other services.....	15,000	56,000	+41,000
Payment to "National Institutes of Health management fund".....	78,000	98,000	+20,000
26 Supplies and materials.....	35,000	40,000	+5,000
31 Equipment.....	39,000	31,000	-8,000
41 Grants, subsidies, and contributions.....	25,000,000	32,800,000	+7,800,000
Subtotal.....	25,685,000	34,002,000	+8,317,000
Deduct quarters and subsistence changes.....	-----	-2,000	-2,000
Total, obligations.....	25,685,000	34,000,000	+8,315,000

TRANSFER OF RESEARCH CENTERS FOR AGING AND CHILD HEALTH

Mr. FOGARTY. While most of the justifications are very general you do mention two specific programs to be transferred—centers for research on aging and in child health now financed by the Institute of General Medical Sciences.

Will you describe the centers that are to be transferred and tell us where they are located, and what you hope to accomplish next year?

Dr. ALDRICH. Mr. Chairman, both of these centers are transferred and are being integrated into the structure of the new Institute. Both the aging center and the center for research in child health were established administratively as focal points, mainly for information on these two pertinent subjects. The small staffs of these two centers are now functioning within the new Institute and are providing leadership in both these areas which are a part of the main effort of the new Institute.

RESEARCH ON AGING

Mr. FOGARTY. I hope that you are more successful than the Department of Health, Education, and Welfare has been over the years in the overall problem of aging. They have not done a very good job—I am talking about Health, Education, and Welfare as a whole—in my opinion, and still are not doing a very good job with the current approach.

What are you going to do in this research center for aging?

Dr. ALDRICH. Well, our plan, Mr. Chairman, is to stimulate and expand research and study the research training in gerontology which is the basis of aging. We are interested in studies of the entire process of human development as a continuum so that events in early life can be related to important health problems of the aged. Many of the roots of aging appear early in life, but do not manifest themselves as significant health problems of the aged for several decades. Identification of these changes at an early period may permit later health problems from occurring through appropriate therapeutic measures.

In addition, we plan to encourage intensive research into rare individuals in childhood who have very precocious aging as exemplified by an experiment of nature known by the term "progeria." These children show extensive aging of virtually all systems beginning soon after infancy.

LEGISLATIVE HISTORY

Mr. FOGARTY. I do not see in the authorizing legislation anything to do with aging. You term human development as being the same thing. There was some problem in the committee or on the floor of Congress at the time this legislation was passed—the aging part of the bill, it seems to me, was removed from the bill. But I am not quite certain of it.

Dr. SHANNON. Could I go into the legislative history, sir? The committee discussed the role of aging and the overall problem of development in a fairly definitive manner and there was no exception taken by any member of the committee to this interpretation of the scope of the institute.

When the bill was considered by the committee, I have been given to understand that it went initially at a time when medical care for the aged was a controversial problem, and it was thought by some of the committee members that to highlight this bill as one oriented to aging, might throw the problem into an unwarranted and unintentional political conflict. For that reason, the term "aging" was dropped without any modification of the legislation. In subsequent consideration of the legislation in the Senate, the action was apparently interpreted as making permissive, rather than mandatory, the inclusion of aging research among the functions of this new Institute. So we felt free to accept this definition of the scope of authority even in the absence of the word "aging" in the basic legislative authorization, primarily because of the legislative history of the authorization.

MR. FOGARTY. Did this colloquy take place on the floor?

DR. SHANNON. No, sir.

MR. FOGARTY. Was it stricken out in the full committee?

DR. SHANNON. It was taken out in the full committee and was not raised as an issue on the floor.

CHILD HEALTH RESEARCH

MR. FOGARTY. What are you going to do in child health?

DR. ALDRICH. Mr. Chairman, we have divided our program in child health into four major parts for identification purposes. Our objective in general is to apply time to the biological process, so I shall enumerate each component, starting first with reproductive physiology. We feel that this is an important subject which requires major expansion of research activity at a very basic level. This includes conception, the process of embryonic differentiation and fetal development, and all of the maternal factors which may bear on the embryo and fetus, as it is developing.

The second element is the birth process itself, with special consideration of the severe stresses and strains and necessary adaptation by both the baby and mother. It is during this period that a number of significant health problems for the infant and for the mother probably occur.

The third area of our child health research program will be a major effort to understand more fully how children develop in our culture. This includes normal physical, intellectual, and behavioral aspects.

We are concerned with all that can be done in prenatal life and childhood to provide a healthy adult, but we must study this whole process of development from the beginning through to the end of life if we are to understand many of our most complicated health problems of today and tomorrow.

In child health this is generally our program.

AREAS OF SPECIAL EMPHASIS IN 1964

MR. FOGARTY. Do you plan any changes in this program during 1964?

DR. ALDRICH. I am not sure I understand your question.

MR. FOGARTY. Changes from what has been carried on in general medical sciences with regard to research in aging and child health—

do you plan any changes in their program when it is transferred to you?

Dr. ALDRICH. We are going to identify several key programs on which we will focus initially. Related research projects will be grouped within the Institute for maximum emphasis. For example, mental retardation will be one of the primary efforts, because we believe that mental retardation is basically a problem in human development. A great many scientists who are interested in this problem believe that this is the proper approach and that it has wide ramifications in many aspects of the field. We are going to bear down very heavily on the subject of prematurity, which is one of the most important health problems of the prenatal period, and I wish to reemphasize our interest in research related to reproductive physiology.

Mr. FOGARTY. What is budgeted for them in 1963 and what is in this budget for 1964?

Dr. SHANNON. We will have to furnish those figures for the record, Mr. Chairman.

(The material follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Tentative distribution of funds relating to mental retardation, prematurity, and reproductive biology for 1963 and 1964

[In thousands]

Research grants	1963	1964
Mental retardation.....	\$2,400	\$5,000
Prematurity.....	1,700	2,000
Reproductive biology.....	3,400	4,000
All other.....	10,500	12,200
Total, research grants.....	18,000	23,200

EXPANSION OF TRANSFERRED ACTIVITIES

Mr. FOGARTY. With regard to the rest of your program for 1964, what part will be a straight transfer from the other Institutes and what part will be new?

Dr. SHANNON. Of the approximately \$34 million, \$26 million will be transferred from the other Institutes as a lateral transfer and approximately \$8 million will be transferred as new program.

Mr. FOGARTY. Of the activities transferred, what ones will be expanded and what ones will be carried on at the same or at a reduced level?

Dr. ALDRICH. I would say of the activities transferred that we would look for a reasonable amount of expansion. The rate is difficult to predict. In general, I think, Mr. Chairman, it is fair to say that these fields have not received the research emphasis that they require; and I think that areas that are being identified and more effectively investigated will expand somewhat in the succeeding years, particularly as additional scientists are trained for this purpose.

Mr. FOGARTY. Tell us about it.

RESEARCH TRAINING IN PEDIATRICS AND OBSTETRICS

Dr. ALDRICH. The best prepared people in clinical departments of our medical schools who are concerned with the areas I have mentioned are in obstetrics, and pediatrics. The scientific disciplines basic to research in these areas include virtually all the medical, biological, and behavioral sciences. I believe that the pediatricians and obstetricians in these departments have not fully participated in the tremendous scientific surge that has gone on for the last couple of decades, and that there is a very real need in the universities to greatly expand their research training in these basic scientific disciplines.

So I think we can look for major efforts by universities and other research centers to improve and expand the scientific training of their pediatricians and obstetricians. Just exactly how extensive this is going to be will depend to a large extent on how the universities identify the magnitude of this problem. But there certainly has been a widespread expression of this need in recent years.

PROJECTS TRANSFERRED FROM CANCER AND NEUROLOGY

Mr. FOGARTY. In order that we may have some specifics in the record, would you take two Institutes—Cancer and Neurology—since their support of this proposed Institute is relatively small, and list the current research project grants that will be transferred to this Institute in 1964 if they are continued?

Dr. SHANNON. We will be glad to do that.

(The material follows:)

TRANSFER OF GRANTS FROM NATIONAL CANCER INSTITUTE TO NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The following research grants now supported by the National Cancer Institute appear to be those with the maximum relevance to the mission of the new Institute of Child Health and Human Development. Therefore, we would propose at this time that this group of grants constitute a list for transfer which may be inserted in the record of the House Appropriations Committee hearings, in response to Mr. Fogarty's request.

Grant number and title

Aging	\$16, 000
6409 Studies on Aging Mouse Skin Grafts.	
Cell growth and differentiation	117, 736
3124 Studies on the Initiation of Cleavage.	
3333 Biochemistry of Cellular Differentiation.	
4552 Studies of the Submicroscopic Structure of Living Cells.	
Embryogenesis	35, 562
2296 Enzymatic Patterns in Growth and Differentiation.	
5936 Nucleic Acid Relationship in Early Embryos.	
Embryology—Teratology	29, 738
5196 Cytology of Growing and Differentiating Cells.	
5287 Effect of Drugs Upon Fetal Hematopoiesis.	
5603 Histochemical Approaches to Diseases of Childhood.	
Human development (prenatal)	79, 849
2451 Growth and Differentiation in Early Human Development.	
Mammalian growth—Development	58, 914
5321 Disturbances of Growth and Maintenance of Tissues.	
5375 A Morphological Study of the Reticuloendothelial System.	
5785 Homologous Skin and Organ Transplantation in Dogs.	
6772 Effects of Irradiation on the Immature Mouse.	

Grant number and title

Regeneration-----	\$39, 927
2236 Comparative Study of Histological and Chemical Features of Early Regeneration	
2913 Xenoplastic Studies of Amphibian Limb Regeneration	
Reproductive biology-----	74, 750
3009 Steroid-Enzyme Relationships in Reproductive Tissue.	
5660 Studies on the Tolerance Induced by Parity.	
5917 Seminal Lipoproteins and Lipolytic Activity in Health and Disease.	
6126 Histology of Human Menstruating Endometrium.	
6819 Histochemistry of Uterine Growth and Pathology.	
Reproductive organ (development)-----	198, 108
2589 The Development of an Improved Prolactin Bioassay Method.	
2897 Steroids and Growth.	
2923 Adrenal and Gonadotrophin Maturation in Childhood.	
4009 Steroid Metabolism of the Human Ovary.	
4121 Disorders of Water Metabolism in Pituitary Disease.	
4240 Effects of Progestins in Human Gonadotrophins.	
4420 Effect of Hormones on Mammary Gland in Organ Culture.	
Total research grants-----	650, 584

TRANSFER OF GRANTS FROM NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND
BLINDNESS TO NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The following research grants now supported by the National Institute of Neurological Diseases and Blindness appear to be those with the maximum relevance to the mission of the new Institute of Child Health and Human Development. Therefore, we would propose at this time that this group of grants constitute a tentative list for transfer which may be inserted in the record of the House Appropriations Committee hearings, in response to Mr. Fogarty's request.

Grant number and title

Aging-----	\$48, 462
2707 Senescence and Neural Metabolism in the Rat.	
2715 Phonation of Adult and Geriatric Populations.	
2748 Ultrastructure of Nerve Cells in Experimental Aging.	
2866 The Eye: Growth and Aging; Changes in Systemic Disease.	
Developmental pharmacology-----	35, 822
2043 Drug Action in Children.	
2952 Pathologic Physiology of Salicylate Intoxication.	
3436 Versene Diagnostic Test for Early Lead Poisoning.	
Embryology—Fetal development-----	267, 647
2786 Importance of Copper in Embryonic Development.	
2238 Mechanisms of Differentiation of Embryonic Cells.	
1590 Vision in Special Environments: Developmental Effects.	
493 Mechanisms in Differentiation of Mesodermal Tissues.	
394 Physiologic and Morphologic Studies on Human Fetuses.	
422 Excessive Vitamin Intake and Congenital Anomalies.	
547 Viral Infections of Embryo.	
931 Mechanisms of Genetically Controlled Abnormal Development.	
951 The Development of the Visual and Auditory Centers in Human Embryos.	
964 Experimental Herpes Simplex Infection in the Fetus.	
1694 Outcome of Pregnancy Complicated by Viral Infection in the First Trimester.	
4416 Physiologic and Morphologic Studies on Human Fetuses.	
Growth and development-----	324, 258
302 The Anatomy of Human Growth and Development.	
2640 Factors in Child Development and Cerebral Palsy.	
2813 A Longitudinal Study of Adolescent Voice Change.	
3609 Mouse and Human Muscle Growth in Diffusion Chambers.	
3972 Hypothalamic Regulation of Feeding and Growth.	

<i>Grant number and title</i>		
Intellectual development-----		\$197, 326
969 Pathogenesis and Treatment of Middle Ear Effusions.		
1586 Development of Distance Perception in Children.		
2126 GSR Measurement of Auditory Discrimination in Children.		
2416 Validation and Normative Studies of Halstead Battery.		
2426 Age Validation of the Halstead Battery of Tests.		
3493 Temporal Sequence Learning and Language Deficiency.		
3887 Delayed Language Development: Auditory Input Factors.		
A Study of the Auditory Input Receptor, Effector, and		
Control Factors Relative to Preschool-Age Children with		
Delayed Language and Speech.		
4268 Sensory Discrimination and Learning in Human Infants.		
Lactation-----		29, 936
2983 Neuroendocrine Control of Lactation.		
3028 Central Afferent Pathways to Neurohypophyseal System.		
Medical genetics-----		84, 158
2543 Chromosomal Pattern in Mongolism and Related Condi-		
tions.		
3327 Chemical Comparison of Normal and Dystrophic Myoglobin.		
3982 Metabolic Studies of Children with Mongolism.		
Mental retardation-----		220, 886
3362 Center for Normal and Aberrant Adaptive Development.		
Perinatal biology-----		134, 137
705 Measurement of Oxygen Tension in Infants.		
3558 The Role of Emotional Stress in Obstetric Complications.		
3635 Effects of Uterine Contractions on the Human Fetus.		
3997 Perinatal Study and Neurological Follow-Up, Infants of		
Diabetic Mothers.		
4109 Factors in Survival of Apneic Newborn Mammals.		
Prematurity-----		72, 680
3124 Preventable Factors in Prematurity—Incidence and Effect.		
Regeneration-----		60, 073
923 Regeneration and Growth Regulation.		
4107 An Investigation of How X-Rays Prevent Regeneration.		
Reproductive physiology-----		76, 462
1386 Hypothalamus in Reproduction and Cortical Activation.		
2691 Mechanism of Energizing Aspect of Hunger or Sex Drive.		
4199 Central Nervous Regulation of Gonadotropin Secretion.		
4400 Relationship of Uterine Secretions to Ovarian Function.		
Total research grants-----		1, 551, 847

PERINATAL STUDY

Mr. FOGARTY. In neurology I can see where the entire perinatal study that is going on could be transferred, under the general guidelines that seem to have been set up.

Dr. SHANNON. That raises a very serious question. The areas of transfer to this Institute will be related largely to the broad program fields that Dr. Aldrich has selected for emphasis during the initial year of this Institute. During the coming year each program will be reviewed from the standpoint of whether it will fit more appropriately in the new Institute or whether it will remain where it is.

Mr. FOGARTY. I was thinking of the perinatal study.

Dr. SHANNON. We have reached a general conclusion. The perinatal study, with its objective of studying 50,000 live births, with approximately 2 years to go, will not be moved. The Neurological Institute will be asked to continue it to completion of the registry of the initial material.

On the other hand, the continuation of certain elements of that program will be very seriously discussed during the fall and winter of next year in order to separate those factors that relate particularly to neurological damage, and those things which can be more closely related to the developmental process; and a separation will be made at that time for purposes of future planning, but the studies themselves will continue in the Neurology Institute until the termination of data collection for the basic study. We are not proposing to transfer program segments into Dr. Aldrich's program unless they fit into predetermined areas of this Institute's concern, and unless they fit in with the plan of the Institute's program development—which I would guess, sir, will take the better part of an additional 2 years.

TRAINED RESEARCH PERSONNEL NEEDED TO IMPLEMENT PROGRAM

In other words, we feel that the deficiencies in the particular scientific areas, which this Institute hopes to overcome, are so great that one must go very carefully and in a very deliberate fashion to obtain progressive involvement of other medical disciplines.

One of the problems in developing this Institute, quite frankly, is that many of the scientific disciplines that have the most to contribute to the program have been bypassed in the course of expansion in medical sciences in the past decade. The greatest contributions may well come from departments that do not now have adequate research space, who do not have adequate research personnel. A slow development of emphasis on research training, will be the most logical approach. And then, I think, we will have a sound program 4 or 5 years hence. It appears more promising if we approach it in this manner, rather than attempting to crash program it, putting everything into the new Institute, and asking people newly on the job to develop it.

BACKGROUND OF LEGISLATION

Mr. FOGARTY. You are still convinced that this was good legislation, establishing this Institute?

Dr. SHANNON. I am convinced, sir, that it is good legislation. I think that my initial reaction was that there were many things sought in the early proposals for the legislation, that could have been accomplished within our present structure—this was when the initial proposal for an Institute of Child Health came from the Department. We felt there was very little in child health, as such, that could not be encompassed in the many programs of the other institutes, but we felt that if the Department was willing to take a broader look at the problems of child health, primarily in the context of development of the human being from birth through differentiation of species, then we felt it could cover an area in which new emphasis should be placed and where we could really put the best brains to work right away. I think that when the Department agreed that this was an advisable modification, then, sir, we were completely behind the development of the Institute.

So our initial rejection of the concept was a rejection of what we felt to be a too highly limited, a too highly targeted program, that could have been accomplished by other means.

RESEARCH ON AGING

I might say, sir, I would like to comment on the role of aging and research in this area, to extend some of the remarks that Dr. Aldrich has made, because I think they are peculiarly pertinent to the long-time development of the Institute.

As Dr. Aldrich outlined in his initial statement, if I can paraphrase what he said, he said that in identifying aging research appropriate to that Institute an attempt would be made to define the elements, the conditions, the biological bases of aging. That is, what happens on the cellular level; what happens on the system level; what happens in a measurable way, that accompanies, and in fact, determines the rate of aging. He would expand that to define broadly some of the psychological characteristics of aging.

Now, the use of the tools of psychology have been very productive in the hands of Dr. Shock in the Baltimore operation, and warrant quite broad expansion. If you then take what Dr. Aldrich said about using the time scale, in terms of understanding biological phenomena when applied to age, he would investigate the role of aging in creating a peculiar susceptibility to disease.

Now, I would like to back off a little and say what is not planned at the present time, because it is in what is omitted here that one sees the broad deficiency in the total study of the aging and the aged.

First, I would say the major problems of the aging and aged today are not in aging per se, but in the preparation and adaptation of the aging and aged individual to a very complex environment. Investigations of this aspect of aging process lie squarely in the field of the social sciences, although the information will have broad implication to the biological processes of the aged.

Now, the present program does not encompass such activities at the present time. We purposely avoided it because it may well be much more profitable for this type of study of the aged to be accomplished within the community environment, and, although experimental in nature, to be conducted by the Bureau of Community Health paralleling their studies of how one delivers services, or how specialized services to the aged can be more effectively utilized on a community basis. This is part of the program of the Bureau of Community Health, if it is established, and if it is not established, then the appropriate segment of the Bureau of State Services.

Now, I would hope that as the program develops, that there will be certain aspects of the activities of the Bureau of Community Health, in the course of some of these problems of the aging population within this communities, that will provide many experimental opportunities for study by Dr. Aldrich's group.

I would say at the present time it would be folly for him, within the present stage of the program, to plan serious program investigations of this type, until after the service aspects of the program are much further along.

I think that we fully realize the deficiency in our handling of the aging problem and the aged in this country, but this Institute does not see an appropriate role to play at this point of time in those particular problems.

Mr. FOGARTY. Thank you. Mr. Denton.

TRANSFER OF FUNDS FROM OTHER INSTITUTES

Mr. DENTON. Now, this is a new agency?

Dr. SHANNON. A new Institute, sir.

Mr. DENTON. A new Institute. All right. And you are asking for \$34 million which is taken from the other Institutes, as is specified on page 3 in the justification?

Dr. SHANNON. Yes, sir.

Mr. DENTON. There is a sum of \$8,030,000 taken from the National Institute of General Medical Science.

Dr. SHANNON. Yes, sir.

Mr. DENTON. Now, are we to subtract the sum of \$8,030,000 from the sum that you are asking for?

Dr. SHANNON. No, sir. What this says is that, if this appropriation is agreed to by this committee and by the Congress, then we will feel free to undertake to negotiate between this Institute and the Institute of General Medical Sciences, to move funds up to as much as \$8 million from the former appropriation to the new one.

Mr. DENTON. Then you are not asking for any additional money for this Institute?

Dr. SHANNON. We are not asking, at this point in time, for any increase in the total budget.

Mr. KELLY. We are asking, Mr. Denton, for a piece of appropriation language which would authorize the transfer of \$34 million. We had two alternative ways of doing this. One was creating an appropriation for this Institute and asking for normal language to do so.

However, at the time the President's budget was prepared, we were not in a position to do so, so we would rather ask for a piece of language which would authorize, out of the total appropriations to the National Institutes of Health, the \$34 million to be devoted to this purpose, rather than for the purposes described in the budget.

Mr. DENTON. You are just going to transfer from the other Institutes up to \$34 million?

Mr. KELLY. Up to an aggregate of \$34 million; yes, sir.

Mr. DENTON. For the year 1963, I understand that you transferred \$8 million to this Institute.

Mr. KELLY. No, sir. In 1963, we have transferred none of these grant funds. Our best estimate is that of the \$34 million that we will transfer in 1964, approximately \$26 million of that will be to continue support of existing programs and \$8 million will be for new programs; but up to the present time, this has not been transferred. The transfers are contingent upon the budget language.

PRESENT METHOD OF FUNDING INSTITUTE

Mr. DENTON. How are you operating this Institute now?

Dr. SHANNON. Well, it has no extramural program at the present time. The Institute now is operating by a grouping of functions that already were established and justified in the other appropriations; primarily these are the Center on Aging Research and the Center for Research in Child Health.

This is the only money that has supported this activity to the present time.

MR. KELLY. I think in reality, we could say, Mr. Denton, what we have done is utilize a very small sum of funds for Dr. Aldrich and his immediate staff to do a planning job, so that on July 1, they will be ready to carry out the program that is being discussed.

SOURCE OF EMPLOYEES

MR. DENTON. How many employees do you have in this Institute now?

DR. SHANNON. Twenty-three, sir.

MR. DENTON. And where did they come from? Other Institutes, or are they new employees?

DR. SHANNON. No; 17 of them came from the already existing Child Health Center and the Aging Center.

MR. DENTON. They were under General Research and Services.

DR. SHANNON. Yes, sir.

MR. DENTON. And do your records show that number is taken away from General Research and Services for 1964?

MR. KELLY. In 1964, that number is still shown under General Research and Services as if it were there, but if you authorize the transfer of \$34 million, then it would be taken out.

MR. DENTON. Now, you are asking for 117 employees.

DR. SHANNON. Yes, sir.

MR. DENTON. Will they be transferred from other institutes?

DR. SHANNON. In the aggregate most of them will, sir; but there will be new employees, in proportion to the aggregate new program, sir.

MR. KELLY. All of them will come from positions which have been requested elsewhere in the budget for the National Institutes of Health.

MR. DENTON. How many new employees will you need for this Institute?

DR. SHANNON. Wholly new employees that are not justified elsewhere?

MR. DENTON. Yes.

DR. SHANNON. We are asking for no new employees that are not justified elsewhere.

COLLABORATIVE STUDIES

MR. DENTON. Under "Direct operation," item 9, you need 40 employees for collaborative study. What do they do? What is that?

DR. ALDRICH. This item of collaborative studies, is partly a response to one of the recommendations of the President's Panel on Mental Retardation, which appears on pages 36 and 39 of their report. There was a specific and rather strong recommendation made, that not only national conferences, but conferences that would attract people who exert leadership in research in other countries, would be held periodically to bring together all of the available information about ongoing research or completed research, and systemize this information for the benefit of those scientists who are working on mental retardation, so the collaborative study in part is to staff conference programs of this type.

MR. DENTON. Why do you need so many employees for conferences?

DR. ALDRICH. We don't need that many just for conferences. This is only one part of the collaborative study effort.

LIBRARY INFORMATION CENTERS

The other reason that we need staff is that we intend to develop some very good information centers. Let me illustrate this, sir.

If you wanted to look up information on the development of the embryo, much of the material that scientists really ought to have, to do the best kind of research, appears in journals not readily available, many of which have not been translated; they are in other tongues. We feel that it is important that contracts be made for translations and to bring all of this information together, in information centers within this Institute, so that the scientific talent of this Nation can go ahead and use it as efficiently as possible.

Mr. DENTON. Is not that literature available over at the library just across the road from you?

Dr. ALDRICH. Some of it is available, but there is much of it that has to be systemized and brought together, and given focus. If a scientist who is working in experimental embryology wants to find quickly all of the information on a given subject, this is quite a job for him, and we want to have it translated and systemized, in order to save him time in his research efforts.

Mr. DENTON. Does not the Medical Library do the same thing?

Dr. ALDRICH. No, sir; it does not.

Dr. SHANNON. No. I might point out this is one of the areas to which increasing attention will be given throughout the National Institutes of Health—developing improved means of facilitating the exchange of information. As the medical literature gets increasingly complex, it becomes increasingly difficult for the individual scientist to become aware of new information as it accrues, even though it may be quite pertinent to his day-to-day activity. While I am not one who believes that this has reached as critical importance as some people have suggested, that books are resting on bookshelves and not being used, simply because people don't know about them.

Nevertheless, I do agree that in the tremendous increase in the scope of medical research, more particularly in the fields of wholly new sciences which can contribute immensely to medical research, the conventional medical literature and the conventional access to the medical literature by the individual medical scientist is not adequate for the effective use of information already available.

Mr. DENTON. This is the first time we have run into this heading, isn't it?

Dr. SHANNON. Yes, sir.

Mr. DENTON. "Library studies," I think this is the first time I have seen it.

Dr. SHANNON. It was mentioned in the Division of Research Facilities and Resources as a quite new function of that Division, sir.

PROGRAM DIRECTION

Mr. DENTON. Item No. 10 is "Program direction." Just what is that?

Dr. SHANNON. Those are funds that are expended to provide for the professional direction of the Institute. This will include, beginning with Dr. Aldrich himself, his key people, such as the individual who

is in charge of the extramural grants and perhaps, as an example, the individual who will be in charge of the program that relates to mental retardation.

REVIEW AND APPROVAL OF GRANTS

Mr. DENTON. I thought you had an item here for review and approval of grants.

Dr. SHANNON. Review and approval is an item that supports the review and processing of applications under the various grant programs of the Institute. Apart from the procedures of what one calls grant management, there are broad problems of program development that require professional scientific talent; it requires travel; it requires negotiation; funds for consultants; all of it veering on the actual concrete evolution of the program that will be proposed by the Institute. These all come in the area of program direction. I might say, too, another important part of that is program analysis, because without analysis, one cannot have adequate direction.

Mr. DENTON. You are not doing any intramural research, then, in this Institute?

Dr. ALDRICH. At the present time; no, sir.

Mr. DENTON. Where do you have your offices?

Dr. ALDRICH. On the reservation at the National Institutes of Health; in building 31. This is our headquarters office to facilitate my communication with the other Directors, and with the Office of the Director.

Mr. DENTON. Which is building 31?

Dr. SHANNON. That is the new office building.

Dr. ALDRICH. And the rest of our staff is in an office building in north Bethesda.

BREAKDOWN OF NEW EMPLOYEES

Mr. DENTON. Now, these 117 employees, would you put in the record, how many of them are Public Health officers; how many are technicians; how many are clerks?

Dr. SHANNON. We would be glad to; yes, sir.

Mr. DENTON. I think that is all.

(The information follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Summary of positions, fiscal year 1964

Activity	Professional		Supporting	Total
	Commis- sioned officer	Civil service		
Program direction.....	5	15	18	38
Review and approval.....		11	28	39
Collaborative studies.....		13	27	40
Total.....	5	39	73	117

Mr. FOGARTY. Mr. Lesinski?

RAISING CHILDREN IN A CONTROLLED ENVIRONMENT

Mr. LESINSKI. Dr. Aldrich, as I mentioned, I have five children, and invariably they get chicken pox; and when they go to kindergarten, they get mumps and one thing and another.

You are talking about child health.

How can you possibly, on God's earth, contribute to a precise child's health unless you can take it from the cradle like they do in Russia, and watch over them constantly?

They have schools in Russia where the child is taken from the parent almost from birth, and raised in these schools.

Dr. SHANNON. While Dr. Aldrich is collecting his thoughts—that is a rough question—I would like to comment on the question, sir, and try to give part of an answer.

Mr. LAIRD. Don't you have to collect yours?

Dr. SHANNON. This would presume that this is a healthy way to handle children, the way the Russians handle them. I would say they consider perhaps that the health of the child relates more to his physical well-being. I think this is one of the problems that Dr. Aldrich faces. He is concerned not only with the problems that relate to normal child development from the biological basis, but also the behavioral, the emotional basis, and when one considers this complex interplay between physical well-being and mental well-being, one has a very serious problem.

Now, this is where I would say that strains and stresses of normal child development in the United States is considerably superior to that of what I would call a more controlled environment.

Now, on the other hand, I think there are many elements that relate to the biological aspects of the healthy child, that are probably much more well taken care of in a highly controlled environment than in the rough and tumble of our everyday family life.

EMOTIONAL VALUE OF LOVE AND TENDER CARE

Mr. LESINSKI. Are not scientists finding out that there is an emotional unbalance of a monkey when he does not have a warm body to come to?

Dr. SHANNON. Oh, yes, sir. There are profound events that condition the emotional life in the development of a child.

Mr. LESINSKI. Are you telling me that the cuddling of a mother or parent of the child is the best thing for a child, emotionally?

Dr. SHANNON. Well, sir, I can only say this. That the former sterile atmosphere of the hospital of 20 years past has given way to a much more human approach to both the well or the sick child, based on a very practical finding. When one takes care of children in an objective, scientific fashion, devoid of any emotional outlay, one has serious difficulty with both the well and the sick child.

I think, beginning in the thirties, the nurses in every good hospital in the country recognized that they must in part attempt to satisfy this need and, in fact, it is considered so important that they must chart when they have fondled the child, paid some personal attention to it. They will generally note on the chart: TLC and the time. This is Tender Loving Care. This is an important aspect of child development.

It is not unimportant, and the thing is, this phrase, TLC is now common to every hospital chart in every good hospital in the country.

MR. LESINSKI. Isn't that one of the reasons, that there is more of an emotional disturbance in America, or a highly civilized community, than there is in a less civilized community?

DR. SHANNON. Well, sir, I just would not be in a position to answer that.

BREAST FEEDING

MR. LESINSKI. Isn't that because of the fact that the breast feeding of a child brings more of a feeling for its parents, than from a bottle. Isn't a bottle-fed baby more apt to be left alone?

DR. SHANNON. When you get to questions like that, I will direct that question to Dr. Aldrich.

MR. LESINSKI. So, therefore, Dr. Shannon, in all fairness, again I repeat, your intentions are proper and of magnitudinal importance to America but the answer is already there. That is what I am driving at, constantly, since I sat on this committee.

DR. SHANNON. The answers are——

MR. LESINSKI. The answers are there. We are talking about one subject here, right now, of childhood.

DR. SHANNON. Yes. I assure you that we would agree that a great many of the answers are there.

MR. LESINSKI. Therefore, do you or do you not agree with me that a breast-fed child is a happier child than one fed with a bottle?

DR. SHANNON. Oh, I mistook your question. I am not in a position to have a professional judgment on that, sir. As I say, I would prefer that you discuss that with Dr. Aldrich.

MR. LESINSKI. Dr. Aldrich?

DR. ALDRICH. I really think it is precisely this kind of a question that we would like to have answers to. There are a great many different opinions, not just in this country, but in other countries, as to the value of breast feeding, and you can get a good deal of discussion about how long it should persist—whether people should nurse their infants until the infant is 2 years of age; or whether it should stop at 3 months, and so forth. But when it comes down to the brass tacks of actually knowing the relationship between nursing one's infant, and what that infant is or does, let's say, when it is 25 years of age, or when it is 10 years of age, we find that we really do not have this kind of longitudinal data study.

This is precisely where the term I used of "time applied to biology," really begins to have some meaning. It is this sort of longitudinal study of normal populations which I personally think will give us the answers to the very cogent question that you ask.

MR. LESINSKI. So children require a bottle at 4 years of age, because they are so emotionally upset, they have nothing to come to. Parents are cold to them. Therefore, they get hold of the bottle.

Off the record.

(Discussion was had off the record.)

MR. LESINSKI. This is on the record.

DR. ALDRICH. No, we do not have a long-term answer.

MR. FOGARTY. Mr. Laird.

NEW LEGISLATIVE AUTHORITY

Mr. LAIRD. Doctor, what new authority was provided in the authorization to establish the Institute of Child Health and Human Development?

Dr. SHANNON. If I may answer that question, Mr. Laird, fundamentally no new authority has been added as such but rather the new legislation and legislative history of a well defined authority provide a point of program emphasis that we feel is important.

Now, when I say "no new authority" I mean substantively, in terms of authorization for awarding research grants or fellowships.

Mr. LAIRD. I cannot find any new authority.

Dr. SHANNON. The new authority is the authority to establish an institute and a National Advisory Council, which in the old authority is precluded except in terms of disease categories. The new authority relates to the ability to create an institute structure which will provide program emphasis that is difficult to obtain by any other device.

Mr. KELLY. But, specifically, the President, in his desire for this new institute, had to seek authority from the Congress to do so. The existing legislation did not permit such an organizational arrangement.

Dr. SHANNON. That is right.

DISADVANTAGES OF INCOMPLETE JUSTIFICATION

Mr. LAIRD. As I understand it, you are going to submit revised budget tables showing 1963.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. These justifications must have been drawn up in an awful hurry.

Dr. SHANNON. It was not drawn up in a hurry. It was drawn up with inadequate information relative to the specifics of the program direction. At the time that the original justification was drawn up, a survey had been made by the institute of programs that could logically be transferred, and effectively transferred, to the new institute, but no program decision was made, as to what would be transferred.

Mr. LAIRD. Have those decisions been made, yet?

Dr. SHANNON. By and large, yes, sir.

Mr. LAIRD. Can you give us a listing of them?

Dr. SHANNON. Well, Mr. Fogarty has asked that we do that.

Mr. KELLY. As I understand it, it has been agreed that we will include in the record, the comparable 1963 program, and the 1964 program.

Mr. LAIRD. This gets in the record after the hearing is all over. We never get a chance to ask any questions that these comparisons may raise in our minds. Coming in with a set of justifications like this, gives little opportunity for a real hearing on the budget of this new Institute. We really won't have a hearing this year. Isn't that correct?

Dr. SHANNON. Well, sir, the main criteria for identifying the discrete grants and the discrete training activity which will be transferred have been covered in the statement here that is in Dr. Aldrich's

comment on the program areas that will be emphasized during the correct?

It might be that Dr. Aldrich might point out again, what those areas are.

Mr. LAIRD. In terms of dollars and cents for specific projects, he does not have this information available now.

Dr. SHANNON. No, sir. Not in those terms.

Mr. LAIRD. That is going to be supplied later. Is that right?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. It is difficult for me to tell if this new Institute is created to centralize all activities in this area, or just add another Institute.

Dr. SHANNON. Well, the new Institute was created to provide the focus that had not been created previously within our existing legislative authority; and second, partially from the program that had been developed previously, we have selected these program areas which will now be transferred to this Institute and emphasized during the first year of its development.

RELATIONSHIP WITH CHILDREN'S BUREAU

Mr. LAIRD. What Children's Bureau activities have been transferred?

Dr. SHANNON. None, sir.

Mr. LAIRD. There are none of the Children's Bureau activities that are transferred to this?

Dr. SHANNON. No, sir. We have had very good working relationships with the Children's Bureau over the years. There are not at the present time, in the Children's Bureau, programs that overlap those of the National Institutes of Health, nor is there any program in the National Institutes of Health more normally conducted by the Children's Bureau. So that when one discusses the possibility of transfer, from existing appropriations into new appropriations, we are not in conflict with the Children's Bureau nor does this raise any new problem for us.

PERINATAL STUDY

Mr. LAIRD. Well, isn't the entire collaborative research study in the perinatal field transferred to this?

Dr. SHANNON. No, sir. The entire perinatal study is left in the Neurology Institute. It will not be touched by this action. But there will be a serious attempt during the coming year to see what elements over the long haul will be more suited to this appropriation than to its continuation in neurology. In the collaborative research program, as it is outlined here, the aggregate of \$400,000, is for the contract of certain rather important conferences, seminar work, seminars and the like, in areas of mental retardation.

Mr. LAIRD. Is this the perinatal study?

Dr. SHANNON. No, sir. Just the broad, general field of mental retardation; the perinatal study will get certain specific answers of a biological sort by investigating some 50,000 births; examining the mother and studying the pregnancy from 3 to 6 months prior to birth, and the child for 5 to 10 years subsequently. This is a highly specific study within itself.

Mr. LAIRD. Well, this is being transferred, isn't it?

Dr. SHANNON. Not at the present time, sir. The 50,000 births will have been completed within about a 2-year period, and we feel that it is much better to leave that in neurology for the completion of that phase of the work.

Mr. LAIRD. It seems to me this unquestionably is in the area of child health and human development.

Dr. SHANNON. It is, sir.

Mr. LAIRD. I cannot understand what is being transferred and what is not being transferred.

Dr. ALDRICH. Could I help illustrate with an example of how this seems to be working out, sir?

The collaborative study has been going on for a sufficient length of time now so that many of the research groups that are participating in it have identified some specific problems that they believe require more intensive research. They are saying, in effect, "Here are some areas that we have uncovered, which are likely to be productive and need attention," but at the same time, they have to keep their mind on the business of completing this long study that they started out to do.

One of the areas—I am just picking one important area—that they all seem agreed upon, is the problem of prematurity. In other words, we should turn more research emphasis on the question of why babies are born prematurely.

Prematurity is an important contributing factor to mental retardation. I would say that one thing this Institute could do immediately is to beef up the premature research program, on a considerable basis, because these other men and women who are working on the collaborative project have their work cut out for them with the task at hand.

We also need to train a considerable additional number of pediatricians and obstetricians in some of the related scientific disciplines so they have the tools to come to grips with this important problem of prematurity.

Mr. LAIRD. Still, I do not understand why the perinatal study is not being transferred to this proposed institute.

Dr. SHANNON. The perinatal study is a specific, collaborative protocol that envisages the need of data of some 50,000 births. This will be completed within the coming 2 years. The total administrative apparatus, the total organizational range of the complex is a very large enterprise.

Mr. LAIRD. That is true of a lot of the other things being transferred too, isn't it?

Dr. SHANNON. No, sir.

BASIS FOR TRANSFERRING PROGRAMS

Mr. LAIRD. How do you arrive at this \$34 million? You must be making quite a few transfers.

Dr. SHANNON. We are, and the details of those transfers by Institute, I can give you now.

Mr. LAIRD. I don't want to belabor the question, but I can't see the consistency of what you transfer and what you don't.

Dr. SHANNON. The point I mean to make is that the conduct of that study is a very complex thing in itself.

The transfer of this total apparatus to Dr. Aldrich would accomplish nothing at this point in time.

HEW AGENCIES DEALING WITH JUVENILE DELINQUENCY

Mr. LAIRD. How many agencies in the Department of Health, Education, and Welfare are working on juvenile delinquency, Mr. Kelly?

Mr. KELLY. Quite a few, sir. We have a special program.

Mr. LAIRD. It seems to me you have almost every agency in your Department doing work in this area.

Mr. KELLY. I would like to comment on that, if I might. I would be glad to give you both a list.

Mr. LAIRD. We have the Justice Department going into it in a big way. I have not gone over the Agriculture Department justification this year, but I expect they are doing work on juvenile delinquency.

Some people thought this new Institute was surely going to get into juvenile delinquency, too.

I am sure there are 15 or 20 different agencies that are in this field. How many of them are in your Department?

Mr. KELLY. Quite a few, and at your request I will be glad to include a statement in the record, identifying each of them, but, offhand, I can tell you that we have an organization dealing with the problems of juvenile delinquency that administers grants. It is part of the new Welfare Administration. We have an interest in this program in the Children's Bureau. We have an interest in this program in the Bureau of Family Welfare.

Mr. LAIRD. That first one is the one that made the grant up in New York?

Mr. KELLY. Yes. They made a grant to the organization called ACT in Harlem.

The Bureau of Family Welfare is interested in this problem, because of the aged and dependent children's program. We have a significant interest in the problem in the U.S. Office of Education; and there are several areas of the Public Health Service that are interested in this, including the National Institutes of Health, and, in particular, the National Institute of Mental Health.

There is an interest in this, in the Bureau of Community Health, but it seems to me that it would be a mistake to conclude that there is a noncoordinated multiplicity of duplicating activities because we find it in several places, because it seems to me it is a problem.

COORDINATION WITH OTHER DEPARTMENTS

Mr. LAIRD. What kind of coordination does the 4-H in the Department of Agriculture have with the juvenile delinquency program?

Mr. KELLY. The President has created a Committee at the level of the Cabinet, for the purpose of coordinating all activities of the Federal Government.

Mr. LAIRD. Did they meet twice this year?

Mr. KELLY. No, I think not. As a matter of fact, they have a full-time staff.

Mr. LAIRD. Do you mean they met more than twice this year?

PRESIDENT'S COMMITTEE ON JUVENILE DELINQUENCY

Mr. KELLY. Well, each of the Cabinet members that are represented on the President's Committee has a full-time alternate, that meet as frequently as once a week or more frequently, and they are dealing with this problem, which involves, among other things, identifying what is being done; how effectively it is being done; and what gaps exist; and recommending to the President programs that deal with the gap areas. In addition to this Government-wide coordination, there is, at the departmental level, a committee that deals with juvenile delinquency. Among other things, we submit to this Committee each year, a report of all of our activities, and the amount budgeted for each of them to identify the extent of our interest in the field of juvenile delinquency, because of the Committee's special interest in it and the extent to which we think we are effectively dealing with the problem.

I do not think this constitutes a multiplicity of overlap and duplications; on the contrary, I think it is a marvelous thing that we have set up a piece of machinery that identifies all of the facets of the problems that deal with juvenile delinquency, and a recognition of the need to bring in each of the disciplines, and each of the systems to make their contribution toward a solution of the overall problem.

Mr. LAIRD. Juvenile delinquency must have a lot of popular appeal for the budget officers, because as you go through the justifications of the various agencies, one after another refer to their activities in juvenile delinquency. I think we are getting to the point where we are going to have to set up a committee to coordinate the coordinators.

It seems to me that this Institute might be able to serve a very useful purpose in the area of juvenile delinquency if it could bring together the activities of the agencies that are working in this area.

HEW JUVENILE DELINQUENCY PROGRAMS

Mr. KELLY. I should think these areas would be much broader than the area of health-related research, but that they will be interested in these aspects; that is, health-related research.

Mr. LAIRD. Will you put in the record at this point the total amount spent on juvenile delinquency, by agency, in your Department for the last few years and the amount budgeted for 1963 and 1964?

Mr. KELLY. We will, sir.

(The information follows:)

Obligations for programs on juvenile delinquency

Agency	1960	1961	1962	1963 estimate	1964 estimate
Office of Education.....	\$79,716	\$35,906	\$36,722	\$170,000	\$766,518
Vocational Rehabilitation Administration.....	52,960	117,639	134,295	169,720	141,006
Public Health Service: National Institute of Mental Health.....	1,511,000	2,781,000	5,170,000	7,140,000	8,040,000
Welfare Administration:					
Children's Bureau.....	208,588	224,665	279,438	347,134	371,055
Juvenile delinquency and youth offenses.....			6,365,567	5,810,000	13,200,000
Total.....	1,852,264	3,159,210	11,986,022	13,636,854	22,518,573

MENTAL RETARDATION RESEARCH

Mr. LAIRD. Now, will all the research in mental retardation be transferred to this new Institute?

Dr. ALDRICH. We expect, sir, to respond, as much as we are able to, to the recommendations of the President's Panel which are very extensive and very specific.

Mr. LAIRD. Certainly they are not transferred this year, according to this justification.

Dr. SHANNON. May I answer the question?

The plan is not to transfer all programs relating to mental retardation to this Institute. Certain areas, relating to the role of brain damage and the like, will be continued in neurology. Those areas that relate to problems of mental illness will be continued in mental health. We will have three major program components. Specialists in mental health; in neurology; and in child health and development.

Mr. LAIRD. Let's put in the record at this point all agencies of the Department dealing with mental retardation; and the amount that is going to be transferred to this Institute.

Dr. SHANNON. We will be glad to do that, sir.

(The requested information follows:)

A FINANCIAL SUMMARY OF THE MENTAL RETARDATION PROGRAM OF THE U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE FOR FISCAL YEAR 1963 AND 1964

NOTE.—A variety of programs administered by the Department of Health, Education, and Welfare relate to the problem of mental retardation, either in whole or in part. The following table contains estimates of the new obligational authority for mental retardation activities in the present fiscal year and the amount proposed for fiscal year 1964 in the President's budget.

Also included in the table are the amounts relating to mental retardation in the administration's legislative proposals as contained in the President's special messages to Congress on mental illness and mental retardation (Feb. 5, 1963) and on education (Jan. 29, 1963).

[New obligational authority in thousands of dollars]

Agency and activity	Fiscal year 1963	Fiscal year 1964			Increases (1964 total over 1963)
		Proposed activities under existing authority	Proposed new legisla- tion	Total	
PREVENTION AND TREATMENT (INCLUDING RESEARCH, TRAINING AND SERVICES)					
Public Health Service:					
National Institutes of Health:					
National Institute of Mental Health.....	7,288	18,291	-----	18,291	11,003
National Institute of Neurological Diseases and Blindness.....	15,839	17,893	-----	17,893	2,054
National Institute of Child Health and Human Development.....		¹ (3,200)	-----	¹ (3,200)	¹ (3,200)
Construction of research centers in human development focused on mental retarda- tion.....		0	6,050	6,050	6,050
Bureau of State Services: ²					
Neurological and sensory disease program.....	290	1,000	-----	1,000	710
Dental services and resources.....	143	105	-----	105	-38
Subtotal—Public Health Service.....	23,560	37,289	6,050	43,339	19,779
Welfare Administration:					
Children's Bureau:					
Maternal and child health services.....	1,665	2,665	500	3,165	1,500
Comprehensive maternity care.....			5,100	5,100	5,100
Research relating to maternal and child health and crippled children's services.....			500	500	500
Crippled children's services.....			500	500	500
Salaries and expenses.....	106	177	-----	177	71
Bureau of Family Services: Salaries and expenses.....	20	25	-----	25	5
Subtotal—Welfare Administration.....	1,791	2,867	6,600	9,467	7,676
Vocational Rehabilitation Administration:					
Grants to States for basic support, and extension and improvement of rehabilitation services.....	3,550	5,400	2,350	7,750	4,200
Research and training.....	1,225	3,235	-----	3,235	2,010
Salaries and expenses.....		47	175	222	222
Subtotal—Vocational Rehabilitation Admin- istration.....	4,775	8,682	2,525	11,207	6,432
Office of Education:					
Training leadership personnel for teaching of mentally retarded children.....	1,000	1,000	-----	1,000	0
Cooperative research program (including learn- ing research) and new educational media re- search (National Defense Education Act).....	517	1,081	-----	1,081	564
Salaries and expenses (exceptional children pro- gram).....	61	129	-----	129	68
Special projects to improve education in slum and depressed areas.....			20,000	20,000	20,000
Teaching of handicapped children.....			5,000	5,000	5,000
Subtotal—Office of Education.....	1,578	2,210	25,000	27,210	25,632
Departmental program: Grants to assist States in planning for mental retardation.....			2,200	2,200	2,200
Total—Prevention and treatment.....	31,704	51,048	42,375	93,423	61,719

¹ Included in National Institutes of Mental Health Proposed Budget for fiscal year 1964. To be transferred to National Institute of Child Health and Human Development during operating year fiscal year 1964.

² Since 1958 the Public Health Service has been authorized, under the hospital and medical facilities construction program, to assist in the construction of facilities that provide an active medical diagnostic and treatment program for the mentally retarded. Since 1958, a total of 37 such projects have been approved, of which 11 are in operation, 20 are under construction, and 6 have received initial approval. It is not possible at this time to make an estimate of the funds that will be used under this program in fiscal year 1964.

FUNCTIONS OF VARIOUS PARTS OF DEPARTMENT IN CHILD HEALTH FIELD

Mr. LAIRD. It seems to me that by setting this Institute up on an age basis, instead of the categorical basis of the various diseases as in the past, may lead to setting up the Institute for the Middle-Aged

and one for the aged. Since we also keep the ones set up by disease category, pretty soon we will have these Institutes going in so many different directions, we will have to set up another one of these coordinating committees in order to keep straight what each one is supposed to do. It bothers me a little bit.

Do you have anything in writing, defining the functions of the various departmental agencies in this field of Child Health and Human Development?

Dr. SHANNON. Yes, sir. We would be glad to make it available. (The information follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The new Institute is designed to coordinate programs of the present disease category institutes in the fields of child health and human development and to stimulate new interest and effort in these important research areas.

The Institute's attention will be focused not on any one disease or part of the body, but rather on the whole person, with its complex of health problems and requirements. There will be emphasis, for example, on the special health status and needs of particular segments of the population—e.g., infants, adolescents, expectant mothers, and aged persons—with common health problems which lend themselves to intensive study.

The program of the new institute will also give major attention to the study of the continuing process of growth and development that characterizes all biological life—from reproduction and prenatal development through infancy and childhood and on into the stages of maturation and aging.

Specifically, the program of the National Institute of Child Health and Human Development will encompass research and training in the following broad areas:

1. The biological and physiological aspects of the processes of human reproduction, growth, and development. Studies of genetics, comparative anatomy, physiology, and biochemistry will be supported only in relationship to the problems of child health and human development.
2. Studies in the prenatal and perinatal period in human development, from conception until shortly after birth.
3. Obstetrical and pediatric problems not directly related to the specific disease interests of the other Institutes.
4. Studies of the process of maturation, including physical, intellectual, and social development, with emphasis on the behavioral aspects and on normal development.
5. Studies in special problem areas such as mental retardation.
6. Studies in the biological, medical, and behavioral aspects of aging.

Despite the deliberate emphasis on child health research and aging research in the program of the proposed new Institute, the existing categorical institutes would continue their primary responsibility for research in their particular disease categories with respect to children and elderly people as well as other segments of the population. For example, the study of leukemia in children would remain in the National Cancer Institute, and the National Institute of Mental Health would continue to be responsible for research into schizophrenia in children.

No curtailment or transfer of the research interests and functions of the Children's Bureau in the field of child health and development is contemplated. To avoid any overlapping of efforts, a fairly detailed agreement has been worked out delineating the respective areas of interest of the Public Health Service and the Children's Bureau in the field of child health research. Under this agreement the Children's Bureau will concentrate on improving the development, management, and effectiveness of maternal, child health, and crippled children's services. The research programs of the Public Health Service in this area will be directed toward the development of new knowledge relating to the health problems and requirements of children and the phenomena of human growth and development. As a further means of assuring necessary coordination, it is planned to have a representative of the Children's Bureau serve as an ex officio member on the advisory council for the new Institute of Child Health and Human Development.

Dr. SHANNON. The primary thing we would refer to the committee is our own description to the Department as to what programs one might expect to be accomplished.

I am sure the Department agrees to such a submission.

PROCEDURES FOR DETERMINING THE AMOUNT OF TRANSFERS

Mr. LAIRD. Now, in order for one of these transfers to be made, that are outlined here, do you negotiate this with the head of the Institute involved, or do you just do this as Director?

Dr. SHANNON. Well, actually, one would hope that it would be largely on the basis of concurrence of Dr. Aldrich for the new Institute, and the Institute directly concerned; and I would simply concur in the relationship.

On the other hand, if there is disagreement, as there most certainly will be in certain areas, then, after suitable study in my office, a decision will be made, and a recommendation will be made to the Surgeon General.

These transfers must be made at levels above me, and will involve concurrence with the Department and the Bureau of the Budget, won't they, Mr. Kelly?

Mr. KELLY. Yes.

Mr. LAIRD. That is all I have, Mr. Chairman.

ESTABLISHING AGE GROUP INSTITUTES

Mr. FOGARTY. I agree with Mr. Laird. I think there may be an institute for aging set up before very long.

Dr. SHANNON. One of our recommendations to the Department, the reason for our strong support of this Institute, was that the biological-psychological processes of development should be considered as a continuum, and particularly that these problems in the young and the very old are so integrally related that we might combine them.

Furthermore, experimental studies upon which investigations of the aged and the young could be based, are primarily life studies and have relevance to both the young and the old.

Finally, it is quite certain that the happenings in the earliest years of life have a very definite effect on health and happiness in the later years of life, and again, this ties these two programs together.

Now, the difficult thing at the present time, and one of Dr. Aldrich's primary problems, is to stimulate really serious interest in problems of aging.

I am willing to be quite critical of the scientists of this country, in that they have not seen the prospects of successful exploration of aging as a thing in itself.

They have not been fired by the excitement of possible productive procedure.

We have far too few scientists who are addressing themselves to the problem that is important, eventually to all of us, to society as a whole. We would hope that, through highlighting this problem within this Institute and by using the variety of means we have to stimulate and to support research, we can develop strong centers within the university world, which will interest themselves in these problems.

I might say, sir, we have not been successful up to the present time, within the existing administrative structure, in developing these fields.

Mr. FOGARTY. Now, Dr. Aldrich, this is your first appearance before this committee. If there are some things that have been left unsaid that you can think of, and you want to say them now, you go right ahead.

Dr. ALDRICH. Well, Mr. Chairman, I think I have said all that I can directly, under the circumstances.

Mr. FOGARTY. Thank you very much.

TUESDAY, MARCH 12, 1960.

NATIONAL CANCER INSTITUTE

WITNESSES

KENNETH M. ENDICOTT, DIRECTOR, NATIONAL CANCER INSTITUTE
 DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ROBERT E. LEARMOUTH, EXECUTIVE OFFICER, NATIONAL CANCER INSTITUTE

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
PUBLIC HEALTH SERVICE			
11 Personnel compensation:			
Permanent positions.....	7,107	8,107	8,610
Positions other than permanent.....	415	405	405
Other personnel compensation.....	103	168	288
Total personnel compensation.....	7,625	8,679	9,303
12 Personnel benefits.....	760	880	933
21 Travel and transportation of persons.....	377	479	489
22 Transportation of things.....	80	82	82
23 Rent, communications, and utilities.....	214	305	311
24 Printing and reproduction.....	185	207	207
25 Other services.....	27,105	37,364	37,556
Payment to National Institutes of Health management fund.....	8,483	9,594	9,891
26 Supplies and materials.....	1,698	1,240	1,260
31 Equipment.....	999	900	951
41 Grants, subsidies, and contributions.....	61,765	77,423	82,961
Subtotal.....	109,290	137,154	143,943
Deduct quarters and subsistence charges.....	19	19	19
Total, Public Health Service.....	109,271	137,135	143,924
ALLOCATION TO VETERANS' ADMINISTRATION			
11 Personnel compensation:			
Permanent positions.....	505	646	669
Positions other than permanent.....	99	140	144
Other personnel compensation.....	1	1	7
Total personnel compensation.....	604	787	820
12 Personnel benefits.....	42	54	57
21 Travel and transportation of persons.....	91	128	128
23 Rent, communications, and utilities.....	1	1	1
25 Other services.....	4	5	5
26 Supplies and materials.....	39	41	41
31 Equipment.....	200	195	188
32 Land and structures.....	2		
Total, Veterans' Administration.....	983	1,211	1,240
Total obligations.....	110,254	138,346	145,164

Personnel summary

	1962 actual	1963 estimate	1964 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions.....	1,283	1,313	1,336
Full-time equivalent of other positions.....	64	62	65
Average number of all employees.....	1,153	1,257	1,312
Number of employees at end of year.....	1,291	1,325	1,350
Average GS grade.....	6.7	6.7	6.7
Average GS salary.....	\$6,057	\$6,354	\$6,413
Average salary of ungraded positions.....	\$3,843	\$3,949	\$3,949
ALLOCATION TO VETERANS' ADMINISTRATION			
Total number of permanent positions.....	93	114	114
Full-time equivalent of other positions.....	9	12	12
Average number of all employees.....	92	116	116
Number of employees at end of year.....	108	132	132
Average GS grade.....	5.2	5.2	5.2
Average GS salary.....	\$4,992	\$5,125	\$5,125

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	\$51,794	\$61,165	\$65,253
(b) Fellowships.....	2,139	4,788	5,188
(c) Training.....	7,832	11,470	12,520
Total, grants.....	61,765	77,423	82,961
2. Direct operations:			
(a) Research.....	14,558	16,308	17,241
(b) Collaborative studies.....	14,754	41,481	42,120
(c) Review and approval of grants.....	1,324	1,772	1,969
(d) Program direction.....	842	1,105	823
(e) Cancer research facility.....	385	257	50
Total, direct operations.....	31,863	60,923	62,203
Total program costs funded ¹	93,628	138,346	145,164
Change in selected resources ²	16,626		
Total obligations.....	110,254	138,346	145,164
Financing:			
Comparative transfers to other accounts.....	7,765	10,317	
Unobligated balance brought forward (—).....	—692	—307	—50
Unobligated balance carried forward.....	307	50	
Unobligated balance lapsing.....	25,104	7,279	
New obligational authority.....	142,738	155,685	145,114
New obligational authority:			
Appropriation.....	142,836	155,742	145,114
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (—).....	—98	—57	
Appropriation (adjusted).....	142,738	155,685	145,114

¹ Includes capital outlay as follows: 1962, \$852,000; 1963, \$1,095,000; 1964, \$1,144,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$1,113,000 (1962 adjustments, \$4,447,000); 1962, \$22,186,000; 1963, \$22,186,000; 1964, \$22,186,000.

GENERAL STATEMENT

Mr. FOGARTY. Dr. Endicott, we will place your complete statement in the record and you may summarize it for us.
(The prepared statement follows:)

Mr. Chairman, and members of the committee, in hearings over the past several years, and through special reports submitted from time to time, the committee has been kept abreast of some rather rapid and exciting developments in the more promising areas of cancer research. In pursuing these opportunities and leads, which I should like to describe in some detail, we have continued to evolve research programs and to marshal our resources of staff and facilities to carry them forward.

First, allow me to take note of several important staff changes that have taken place during the year. Dr. Stuart M. Sessoms, who had been Associate Director of the National Cancer Institute for Collaborative Research, was appointed Deputy Director of the National Institutes of Health. Dr. Paul Kotin, who had been a professor of pathology at the University of Southern California's School of Medicine in Los Angeles, joined the Institute as Chief of the Carcinogenesis Studies Branch. Two staff promotions were made to fill key positions: Dr. Alfred S. Ketcham was appointed Chief of the Surgery Branch to succeed Dr. Robert R. Smith, who is now at Emory University, and Dr. Walter E. Heston was appointed Chief of the Laboratory of Biology to succeed Dr. Howard B. Andervont, who is now scientific editor of the Journal of the National Cancer Institute. The position of Assistant Director of the Institute, which had been vacant for some time, was filled with the appointment of Dr. Robert W. Weiger, a former clinical associate in our General Medicine Branch.

The reassignment of Dr. Sessoms as Deputy Director of the National Institutes of Health was a serious loss to the National Cancer Institute, although a well-deserved honor for him. We have been unable to fill this vacancy since it occurred last August 1, and I regret to say that we are also soon to lose another member of the Institute's senior management staff, Dr. Michael B. Shimkin, Associate Director for Field Studies, who has informed me of his intention to retire from the Public Health Service this June. Dr. Shimkin has made many outstanding contributions during his Public Health Service career and is one of the world's leading experts on cancer.

I should also like to take note of several honors bestowed on members of the Institute's professional staff during the year. Dr. Thelma Dunn of the Laboratory of Pathology was a recipient of the second annual Federal Woman's Award in honor of her distinguished career in experimental cancer research. Dr. Howard B. Andervont, scientific editor of the Journal of the National Cancer Institute and former Chief of the Laboratory of Biology, was among those given the National Civil Service League's Eighth Annual Career Service Award for outstanding performance. Dr. Wilhelm C. Hueper, Chief of the Institute's Environmental Cancer Section, shared with a Russian scientist an award of \$10,000 given by the United Nations General Assembly for outstanding scientific research on environmental causes of cancer.

In order to move ahead on new research leads, which I shall describe, it has been necessary to organize key members of our staff as committees to develop and implement programs, and as task forces to make concerted investigations in areas of high import. The Institute's top-level management staff has been organized as a scientific directorate. This body advises the Director on the research and related programs, coordinates operations, and gives final review to contract proposals.

We have established two standing committees which will develop programs for research on cancer causation and prevention and on diagnosis and treatment. They are also performing preliminary screening of contract proposals, a function formerly carried out by various panels and committees of outside advisers, which were abolished to avoid any implication of a conflict of interest. Outside consultants now assist our staff in reviewing contracts on an ad hoc basis only.

We have also organized two task forces, whose memberships include prominent investigators from other institutions as well as Institute staff, to conduct intensive investigation, over a limited period, of leukemia therapy and of viruses as a cause of human cancer.

CAUSATION OF CANCER

The committee is familiar with the fact that scientific evidence accumulated over a number of years, and particularly in the last half-dozen years, has demonstrated that viruses cause many forms of cancer in animals under experimental conditions. In previous hearings we have cited the intramural work of Drs. Sarah E. Stewart and Bernice E. Eddy on the polyoma virus which causes multiple primary tumors in mice, rats, and hamsters. We have also reported Dr. John B. Moloney's discovery of a new virus which causes leukemia in mice and rats. This year, Dr. Frank J. Rauscher reported the isolation of a virus that causes a complex of nonleukemic disease reactions in mice in only 7 days and leukemia in 30 days. Electron microscope studies of the Moloney virus by Dr. Albert J. Dalton and others have demonstrated an important resemblance in shape to certain bacterial viruses whose method of attack is well known.

The large volume of such evidence, coming from a wide variety of scientific disciplines, is so strongly suggestive of a virus-cancer relationship in man that the National Cancer Institute has given active encouragement to research in this area. To date, no human cancer-causing virus has been found. However, we know for example of a group of human viruses that have not yet been linked with specific disease, and some animal viruses that cause bizarre changes in human cells growing in tissue culture. One of the viruses of the latter group, I might add, was found to be a contaminant in some early lots of polio vaccine. Our interest has also been aroused by recent evidence obtained independently by Dr. John J. Trentin, Baylor University, and Dr. Robert J. Huebner, National Institute of Allergy and Infectious Diseases, that some of the human adenoviruses, which cause acute respiratory illness, produce tumors in hamsters.

The present state of knowledge leaves no doubt in our minds that viruses must be studied not only as a single possible cause of cancer in man, but in the whole context of carcinogenesis. The possible interaction of substances in the total environment—such as radiation, chemicals, and viruses—in giving rise to cancer in the population must be taken into account. Already there is laboratory evidence that this can occur in animals. Mice exposed to an infectious virus and the vapors of small amounts of a carcinogenic chemical developed lung cancer. Again, rats whose lung tissue was damaged by a noncarcinogenic chemical developed cancers in the area of healed-over tissue when exposed to a carcinogenic chemical.

To pursue investigations of human carcinogenesis on a scale which will produce conclusive results requires that an adequate groundwork of experimental data be laid. The National Cancer Institute is setting out to do this research on a major scale in three areas—chemicophysical studies, epidemiology, and virology—where parallel activities may cross at certain points and may confidently be expected to merge ultimately in a highly refined and sophisticated study of human cancer causation.

One of these approaches is being taken by the Carcinogenesis Studies Branch which is now under the direction of Dr. Paul Kotin, whose personal research efforts have been mainly in this area. This Branch is undertaking to develop methods for testing carcinogenic chemicals found in the environment and to determine whether a minimum cancer-causing dosage level exists for such agents both in animals and in man. The work will be conducted through intramural investigations, the use of contracts to extend intramural research, and through collaborative studies with other Government agencies.

An interagency project was recently arranged in which the Institute will collaborate with the Atomic Energy Commission on studies of the interaction of radiation and chemicals as a possible cause of cancer in animals, with emphasis on fundamental investigation of the carcinogenic process. This work, which may be expanded later to include the investigation of the roles of viruses in this process is being done at the Oak Ridge National Laboratory under the Atomic Energy Commission contract with the Union Carbide Corp.

Rather closely related to the experimental work of the Carcinogenesis Studies Branch are the epidemiological investigations of the Biometry Branch which are being expanded to include collaborative studies with scientists in other parts of the world. The object here is to observe the statistical changes in cancer morbidity for individuals or groups who move from one environment to another in a change of residence. For example, an Institute scientist reported during the year that smokers who move frequently from one community to another are more likely to develop lung cancer than less mobile citizens and that the risk

is greatest for heavy smokers moving from rural to metropolitan areas and for the foreign-born settling in large cities. A comparative study is being made of the relationship of customs and personal practices to the incidence of cancer of the lung and stomach among the Japanese in Japan, Hawaii, and California. Available information suggests that cancer rates for Japanese immigrants to Hawaii are intermediate between those for the other two groups. A similar collaborative study to learn what factors influence the cancer risk for people who migrate from Poland to the United States is being developed with the Polish Ministry of Health and the National Cancer Institute of Poland. Polish immigrants to this country have a higher risk of cancer of the esophagus, stomach, and uterine cervix than native-born residents.

Finally, in the virology program preliminary spadework has been done in developing necessary research resources, such as virus-defined animals, virus-free cell lines, and viral detection agents. The Virology Research Resources Branch is undertaking to provide through contractual arrangements the large number of animals and cell lines needed by investigators in virus-cancer research, and the Institute is collaborating with the National Institute of Allergy and Infectious Diseases to obtain the required detection agents.

All such resources are mobilized behind the Human Cancer Virus Task Force which we have established under the chairmanship of Dr. W. Ray Bryan, Chief of the Institute's Laboratory of Viral Oncology, to explore selected avenues through which the role of viruses in the induction of human cancer may be elucidated. The task force will undertake the most effective and efficient coordination possible of all required research resources to accomplish its purpose within a given period of time, say 3 to 5 years. It will seek the answers to important specific research questions, and at the end of its period of operation we should know whether to mount new comprehensive research efforts or modify ongoing programs.

Programing for integrated activities on carcinogenesis has produced a number of special problems relating to facilities, and it is our intention to create highly flexible contract resources in or as close as possible to the Bethesda area which will enable our scientists to keep in daily contact with the work and thus exercise, for example, the exquisite control over viruses that is needed in an experimental situation.

I should like to emphasize that carcinogenesis—the induction of cancer by agents, such as viruses, acting either alone or in concert with other agents—is the research area of top priority with the National Cancer Institute. Our efforts in this broad area will utilize appropriate experimental procedures but will be aimed directly at the human cancer problem in an effort to control this disease primarily through prevention.

DIAGNOSIS

Research to discover better ways of detecting and diagnosing cancer has long been an important area. One of the more recent and much needed developments was a simple method for detecting cancers of the kidneys and bladder before symptoms appear. It is a test of urine specimens to check the activity of an enzyme known as LDH, which is regularly abnormally high in persons who have such cancers. Though other serious diseases of kidneys also cause an increase in LDH activity in the urine, these can be differentiated from cancer in a thorough examination. This technique may help reduce mortality from kidney and bladder cancers, which take an estimated 13,000 lives a year.

Diagnostic research has been conducted and supported by the National Cancer Institute for some time. Although we have no present plans to expand this research, we are going to do all we can to refine such projects and make them more effective. A number of possible leads to further investigation have come from the work the Institute has already supported, but to pursue them will require an approach that we are not presently equipped to make. A case in point is the X-ray procedure called mammography, reported by radiologists at the M. D. Anderson Hospital in Houston and the Albert Einstein Medical Center in Philadelphia to be an effective tool for detecting early breast cancer. The procedure is complex, and so far has proved a valuable diagnostic aid only in the hands of experts. Although the technique may be greatly refined and the results standardized to an acceptable level of reliability, the efficacy of the procedure can be ascertained only through long-term study of end results.

The Institute has awarded a contract to the Health Insurance Plan of Greater New York to plan a 10-year study to compare the results of treatment in large numbers of women whose breast cancers were detected through mammography with the outcome for those diagnosed by other means. The ultimate objective is of course to determine whether mammography can lower the mortality rate for breast cancer, which has remained virtually unchanged for 30 years.

In order to strengthen Institute resources for diagnostic research, we are planning to establish a Laboratory of Experimental Clinical Pathology which will conduct investigation and plan and direct extensive field trials and instrumentation projects.

TREATMENT

The committee has been kept well informed, I believe, on the search for new and better drugs for the treatment of cancer. In this ongoing activity we have reached a turning point in the preliminary screening of compounds after an intensive effort of several years. The original three-tumor system animal screen has been broadened, and we have also cut back the volume of materials put through the diversified screen.

We are adding projects to develop antiviral drug screening, on the assumption that viruses will one day be proved to cause human cancer. Success in the effort to find drugs effective against viruses would make this an undertaking of broad significance for the treatment of all virus-caused diseases. Another screen that is being developed is one to find chemicals that will modify the effects of radiation, either by protecting normal tissues or by concentrating in cancerous tissue and potentiating the radiation effect. The results of this research will hopefully permit broadening and diversifying of the screening system so that its reliability for selecting compounds that will be active in clinical trial will be increased.

Simultaneously with the action of reducing the number of compounds screened, we have initiated a study designed to provide leads to identifying new and potentially useful drugs. This study will attempt to discover biochemical defects in human tumors as a basis for the design of more effective drugs. This study may also be able to predict whether it would be feasible to use a specimen of a patient's own tumor as a test system for selecting the drugs that would be of greatest benefit to that individual.

In the clinical area we have an adequate number of studies for the evaluation of drugs in patients. These programs are in the hands of an ample number of collaborating physicians, and the availability of patients is no longer a problem in most areas. I would say, therefore, that the major difficulties in arranging clinical trials of drugs coming out of the "pipeline" which were experienced early in the chemotherapy program have been solved.

New problems are arising, however, as the clinical aspect of the program advances. One of these is the lack of adequate laboratory backup for first phase studies of compounds in man. The development of centers to provide this service in "phase 1" cooperating institutions is essential to the success of the effort to provide more and better chemotherapeutic modalities for the cancer patient. Another problem is the need for more adequate data processing and communication. This may, in fact, become more acute because of the increased amount of reporting required by new legislation pertaining to drug trials. We plan to meet this problem by stationing a physician at the headquarters university of each collaborating clinical trial group to analyze and interpret data to the National Cancer Institute on a day-to-day basis. We also intend to move in the direction of applying more automation in the transmission, analysis, storage, and retrieval of the data and to keep the Food and Drug Administration fully informed on drug development.

There is one segment of the cancer problem in which the outlook for major gains in the months ahead is especially hopeful. This is in the care and treatment of patients who have acute leukemia.

Only 15 years ago, acute leukemia patients almost always died within 3 to 4 months after diagnosis. The first break in this dismal situation came from the Children's Cancer Research Foundation in Boston, where Dr. Sidney Farber showed that the disease could be temporarily suppressed by a drug known as aminopterin, which has since been supplanted by the related compound, methotrexate. A few years later, investigators at what is now the Memorial Sloan-Kettering Cancer Center found that another drug, 6-mercaptopurine, would also produce remissions. The introduction of these two drugs and of cortisone and

related steroids raised the median survival of children with acute leukemia to more than a year.

Until recently, there were no additional improvements. Within the last 2 years, however, a number of new and dramatic advances have been made. On previous occasions, I have mentioned some of these, including the use of platelet transfusions to control hemorrhage, which is a frequent cause of death among acute leukemia patients, and the introduction of a drug known as Methyl-GAG, the first drug to produce more than an occasional remission in patients with acute granulocytic leukemia. The National Cancer Institute, I am proud to say, played a leading role in both of these achievements.

Now two more drugs have come along that produce remissions of acute lymphocytic leukemia, the type that children most often have. One is a periwinkle plant extract called vincristine, and the other an alkylating agent known as cyclophosphamide. Vincristine was developed by Eli Lilly & Co. and immediately found useful for treatment of lymphomas, such as Hodgkin's disease but it was at the National Cancer Institute that its value in acute leukemia was first demonstrated. Cyclophosphamide, developed in Germany, has been used for a few years against other forms of cancer, but it was only recently, in clinical trials conducted under the auspices of the national chemotherapy program, found useful in acute leukemia.

Thus, there are now five drugs (counting steroids as one) that can induce remissions of childhood acute leukemia. This is a distinct advantage, for it is now possible to use drugs in sequence to bring about life-prolonging remissions several times rather than once or twice. In addition, studies of various combinations of the five are already underway in the hope that such an approach will yield even better results.

With respect to supportive treatment for acute leukemia patients, the techniques used so successfully in replacing platelets have been adapted, with encouraging results, for transfusions of white cells, or granulocytes. Because acute leukemia patients often suffer from a lack of granulocytes, they are particularly susceptible to infections, which, like hemorrhages, are often fatal. By collecting granulocytes from patients with chronic granulocytic leukemia, who have a surplus of these cells, and giving them to acute leukemia patients, our staff scientists have been able to cure a number of life-threatening bacterial infections. The great advantage of both platelet and white cell transfusions, of course, is that they offer a way of keeping patients alive long enough for drug treatment to take effect.

These were the developments that prompted us to organize the Acute Leukemia Task Force under the chairmanship of Dr. C. Gordon Zubrod, the National Cancer Institute's Scientific Director, composed of Institute staff members as well as prominent investigators from several other institutions. The objective of this task force is to focus closely coordinated efforts and resources on intensive chemotherapeutic and supportive treatment of the acute leukemia patient.

As its initial projects, the group has undertaken two studies. One is aimed at identifying, and eventually using as a screen, those animal tumors which most accurately predict the effects of drugs in leukemia patients. The other, patterned after the cooperative clinical trials conducted under the chemotherapy program, is a study of platelet-replacement therapy, in which at least five institutions will participate initially. This endeavor represents the first step in an effort to iron out the many technical problems that at present limit the routine use of platelet replacement to only the largest hospitals.

These results certainly seem to demonstrate the validity of our approach in applying intensive effort to the control of a particular type of cancer. We hope to be able in future years to report similar and even more substantial advances.

The request for 1964 is distributed among program activities as follows:

Grants:

Research-----	\$65, 253, 000
Fellowships-----	5, 188, 000
Training-----	12, 520, 000
Subtotal, grants-----	<u>82, 961, 000</u>

Direct operations:

Research-----	17, 241, 000
Collaborative studies-----	42, 120, 000
Review and approval of grants-----	1, 969, 000
Program direction-----	823, 000
Cancer research facility (brought forward)-----	(50, 000)
Subtotal, direct operations-----	<u>62, 153, 000</u>

Total 1964 appropriation request-----	145, 114, 000
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Dr. ENDICOTT. Mr. Chairman and members of the committee, I welcome the privilege of discussing with you the steps we have taken in recent months to pursue the new opportunities and fresh leads that cancer research is constantly providing.

To advise me on research and related programs, to coordinate operations, and to review contract proposals, the Institute's top level management staff has been welded into a scientific directorate. Under it, two standing committees have been established to develop programs for research on cancer causation and prevention and on diagnosis and treatment. We have also organized two task forces, composed of staff as well as prominent investigators from other institutions, to lead intensive investigations of viruses as causes of human cancer and investigate treatment for acute leukemia patients.

Recent findings have prompted us to broaden our research on the causation of cancer to include the effects of viruses alone and in combination with other environmental factors, such as radiation and chemicals. This top-priority research area is now the focus of coordinated intramural investigations in virology, carcinogenesis, and epidemiology, buttressed by research and development contracts, by collaborative studies, and by the work of the newly established Human Cancer Virus Task Force.

To evaluate an especially promising development in cancer case finding, an X-ray technique for detecting early breast cancer, the Institute has given its support to planning work for a 10-year study of the results of treatment following detection of breast cancer by this method, and by other means.

The nationwide cooperative cancer chemotherapy research program, which the Institute administers, has been broadened by the addition of projects aimed at developing screening systems for antiviral drugs and for chemicals that will modify the effects of radiation. An effort to identify biochemical defects in human tumors as a step toward designing increasingly effective drugs has also been initiated.

The Acute Leukemia Task Force has begun work on two projects, including a cooperative-type study of platelet transfusion therapy for hemorrhage. These endeavors and others to follow should make it possible to extend the major advances made in the last 15 years in caring for acute leukemia patients.

INCREASES REQUESTED FOR 1964

In conclusion, Mr. Chairman, the request for the National Cancer Institute for 1964 is \$145,114,000 as compared with the \$138,089,000 available in 1963. The request for 1964 will provide an increase of \$4,088,000 in research grants; an increase of \$400,000 for fellowships; an increase of \$1,050,000 for training; an increase of \$933,000 for direct research, of which \$488,000 is for reimbursement to management fund; and an increase of \$639,000 for collaborative studies. Other smaller but no less important increases are described in the budget justification.

Mr. FOGARTY. Thank you.

I will call on Mr. Lesinski, at this point.

Mr. LESINSKI. Thank you, Mr. Chairman. I appreciate it very much.

DIFFERENCE BETWEEN A VIRUS AND A GERM

First of all, who is capable here of explaining to me the difference between a virus and a germ?

Dr. ENDICOTT. Well, I will try.

The difference between a virus and a germ is like the difference between—

Mr. LESINSKI. Cat and dog?

Dr. ENDICOTT. No. Between Minnesota and the United States.

Viruses are one form of germ. There are other forms that are called germs, too. Bacteria. Some folks would even include some unit cellular parasites as germs. It is a class of germ.

RESEARCH ON CANCER-INHIBITING PLANTS

Mr. LESINSKI. Dr. Terry, do you recall back in about the mid-thirties, where there was, supposedly, a quack doctor, that came from somewhere in Illinois, and found that when horses ate a certain plant on the corner of the field, the growth on their bodies disappeared. I am not in the position to evaluate him. He had supposedly given this plant to people with cancer, and the American Medical Association of Illinois took issue with him. They got him into a lot of trouble. He moved to Texas. He got into a problem with the authorities in Texas, and was put in prison and was jailed and one thing or another.

The only reason I brought the subject up—whether he is right or not, I don't know—but the reason I brought it up is simply this: You are talking about viruses, about experiments. Would it not be fair to the good people of the United States to take this gentleman's experiments originally, and go over them again?

I know the Health Department turned him down at that time, but at this point, because you have the research money and the funds available, and the technicians, can you not take the very basic theories, and go over them again?

Dr. TERRY. You directed that question to me.

Mr. LESINSKI. The reason I directed it to you, I thought you might remember it.

Dr. TERRY. Well, I am a lot older than most people here. Actually, I don't remember the particular instance. Dr. Endicott may know his cancer history well enough to identify the particular individual.

Mr. DENTON. The Food and Drug Administration is the one that investigates these, I believe.

Mr. LESINSKI. Regardless of Pure Food and Drug, whether they do or not, I don't care about that. The important thing that I care about is, the chairman is interested in eradicating cancer.

Now, would it be within your premise to go into this thing all over again?

Dr. TERRY. Mr. Lesinski, this is a constant problem with us, and we have set up a regular routine for evaluating all sorts of claims.

Mr. LESINSKI. Have you evaluated this one?

Dr. TERRY. Well, I am not able to say. I am not certain.

Mr. LESINSKI. The only reason I brought it up, is, I can see a relationship between what he did, and what you are doing here, and if a certain type of foodplant will hold back the growth of cancer—I am not saying it does or it does not, because I do not know—but if it does, it might have relationship to what you are trying to achieve by trying to develop or find such a plant, because, you take the bark of a tree—what do you call that?

Dr. ENDICOTT. Where you get quinine?

Mr. LESINSKI. Yes. This is one thing that was found. Tobacco in some way, was supposed to be good for sores, and various herbs. As a matter of fact, mushrooms, certain type of mushrooms, grown in Germany—found in Germany—are supposed to be good to keep you from having cancer; and what is a mushroom but simply a one-cell element of—what do they call these?

Dr. ENDICOTT. Fungus.

Mr. LESINSKI. Yes. That is all it is.

Now, a doctor out of Detroit, Mich., was trying to develop this mushroom for growth. It was found he could not grow it in a laboratory because of the fact that he could not create the same natural conditions. So he tried to find another mushroom that had the same qualities.

Now, the only reason I am bringing these things out is the fact that I think that, in all fairness to everyone, we should have these things completely explored and developed, if at all possible; all ideas; all thoughts. As was said before, by Dr. Shannon, we have so much knowledge we have not been able to coordinate together.

Now, if you want information about the mushroom, I can give it to you.

Dr. ENDICOTT. I would be very happy to have it, sir.

RESEARCH WITH PLANT EXTRACTS

May I explain to you what we actually are doing in this field? You mentioned plants as having possible action against cancer. There are several plants which contain ingredients that are quite

active against cancer. One of them is currently on the market. It is produced by the Eli Lilly Co. It comes from the plant called the periwinkle. It is an alkaloid which has very considerable activity against several forms of human cancer.

We are currently collecting plants from all over the world, and making extracts of them and testing them, first in mice, with those that look good; then go on finally in our trial in man.

I think—I have forgotten the exact figures—we tested something like 18,000 plant extracts in the past year, of which a great many show some activity. The laboratory group is, at the present time, quite excited about one which comes from a plant in New Zealand.

This is a field that is difficult to explore, because of the long distance involved and oftentimes, the large amount of plant that you have to get, to get enough to work on.

Mr. LESINSKI. At that point, might I interrupt again? Instead of taking those thousands and thousands and thousands of plants, you have millions of types of plants throughout the world, and trying to pinpoint each one, whether it will or will not, would it not be simple to take peoples of the different parts of the world: Poland, Italy, Tibet, wherever it may be, and see if they have—if in that particular area of the world, if there is any amount of cancer; then take that same ethnic group that is transposed to America, and see whether the cancer is increased. Then, when you find the peoples of the world, who have the least amount of cancer cases, find out what their habits are; what their foods are.

Dr. ENDICOTT. We are doing that too, sir. As a matter of fact, to pursue the plant thing, one of our scholars has studied folklore and mythology of other countries, and from this, gets ideas of useful plants. We have actually gone to places like Palestine and collected plants which were referred to in the older literature, and actually found some ingredients in them which have some activity; but I think you have raised a very important area of research, which is to try to study the cause of human cancer by studying man in different environments.

ENVIRONMENTAL INFLUENCE ON CANCER

I would like to tell you, briefly, about several studies that we have going on at the present time on these. As you know, in certain parts of the United States, there tends to be heavy concentration of immigrants from one country or another, and we have made arrangements with the Bureau of Vital Statistics and the Census, and so forth, to study such ethnic groups in the United States—the first, second, and third generations—and also, to study the cancer incidence in their country of origin.

One of these groups is Polish; another is from Great Britain, and perhaps the most elaborate one will turn out to be with the Japanese. We have a unique opportunity here in that we can study cancer incidence in the home island; we can study the transition stage in the Hawaiian Islands; and then the third stage on the California mainland; and the diet and habits, and so forth, of the Hawaiian Japanese are somewhat intermediate between home island and California.

Now, these studies are long term, I can only tell you some of the preliminary impressions and results at this point in time, but it would

appear from the information we now have, that much of the subsequent cancer history is established at a very early period in life, because those who are born, let's say, in Poland and come to the United States, grow up in the United States, grow old and die, their cancer experience is essentially the same as that of the man who stays in Poland; whereas, as the next generation is born in the United States, it has cancer incidence essentially the same as that of other Americans.

Now, to those of us who are interested in possible virus evidence like this, this may suggest, perhaps, infection in early infancy which does not produce anything much then and sort of disappears and results show up a long time afterward.

It might have something to do with some of the areas that Dr. Aldrich will be exploring; something that perhaps happens during pregnancy or something of that sort.

Mr. LESINSKI. May I inject a few thoughts here? I should like to give a long dissertation here but I shall not—my time is limited.

Ever since the central European nations—way before ancient Rome—the people have tilled their soil and have had some of the richest crops in the world, in the central part of central Europe, including Poland, the Czechoslovaks, and so on. They have never used artificial fertilizer and have constantly reverted back to the soil everything they had taken out of the soil, plus. They gleaned the woods and forests of leaves and one thing and another. Every year they moved the outhouse and planted a fruit tree where that house was before. They grew tremendous crops, and used to be the breadbasket of the world.

You say that after they came here, after their descendants were born in America, that their rate of cancer was just as high as anybody else's—as any other nationality—but those coming from the old country, the rate is low, correct?

Dr. ENDICOTT. I would like to qualify that. The overall rate for all kinds of cancer is about the same in the United States and Europe and in Russia. It is when you begin to examine the incidence of different kinds of cancer, that you find the major difference.

For example, the Japanese have a much higher incidence of cancer of the stomach than we have in the United States. We have a much higher incidence of cancer of the lung in the United States than they have in Japan; but these differences tend to cancel one another out so that the overall total rates tend to be about the same.

Mr. LESINSKI. Well, the point I was driving at, in the old country, when a guy had a bad stomach, he went on a diet of greens, and no doctor told him what to do. He had nothing but a sour stomach. If he had an ulcer, he used sauerkraut juice. Of course, this will only take care of certain types of ulcers, which is true.

Now, the point I am driving at is simply this. The rate of cancer is going to increase in proportion to the various types of chemicals used in the body, naturally.

Dr. ENDICOTT. Yes, I think that is probably true.

Mr. LESINSKI. That is the very reason why I was very happy to have the Environmental Health Center come in to study the after effects of these various medications, and so forth.

Now, I am glad that you are studying the relationship between food and cancer, because I think that has a very basic bearing.

Dr. ENDICOTT. We do, too.

Mr. LESINSKI. That is why I brought up this [Hoxie] idea. Whether he hit upon the right plan, I don't know, but basically, I think he has some methods that might cure cancer or growth in the body of a horse. Maybe you can follow up his experience with the same plant, and see what he did wrong. I don't know.

VALUE OF ANCIENT MEDICAL KNOWLEDGE

They talk about modern skin grafting, and so forth. Way back, 400 or 500 years ago, in India, prior to its being taken over by the English, one of the penalties for a crime was cutting off of the Indian's nose. They cut a "V" off of the forehead, flip the skin off, and graft it back on to what was formerly the nose.

In ancient Inca, prior to its being taken over by the Spaniards, they used a three-pronged—not a sharp prong—but a three rounded prong mallet, as a weapon of fighting one another. In other words, like having a big stone at the end of a stick with which they hit the opponents over the head. They perfected brain surgery. I don't mean surgery as we know it today, but they perfected pretty much the incision, going into the brain, and taking out broken bone, and so on, and suturing up the wounds.

Now, true, we are more advanced than they are in that field. I cannot argue that question, but there might be many things that we are using today that can be toxic, harmful to the body, where in years gone by, they had natural means of disposing of these problems, and that is why I brought the subject up. Not because I am right, or the doctors are wrong, please forbid. But if there is a possible way of eliminating the aftereffects of medication I will be very happy to have that done.

Dr. ENDICOTT. So would I, sir, because I am quite sure that we doctors with our new drugs are constantly creating new problems. I think it is an inevitable accompaniment of progress in medicine; you solve one problem and create another.

ESTIMATED UNOBLIGATED BALANCE OF 1963 FUNDS

Mr. FOGARTY. The appropriation for 1963, adjusted for comparative transfers is \$145,625,000 and the request for 1964 is \$145,114,000, a reduction of \$461,000. However, it is estimated that there will be an unobligated balance at the end of 1963 amounting to \$7,279,000, so the budget would provide for an increase in the program amounting to \$6,818,000 if the estimate of unobligated 1963 funds is accurate.

What accounts for the unobligated balance?

Dr. ENDICOTT. The unobligated balance, I think, probably is attributable to a number of factors. Perhaps the area in which we have erred most in our estimates is in the area of training. As short a time as 6 or 8 months ago, my estimates of the need for training for next year were many, many millions of dollars above what they are now.

The demands, the opportunity for investment, which we had expected and hoped to be able to activate simply have not materialized. The reserves which have been taken, so far as I can tell, represent funds that we could not have programed if they had been available. I suppose in part the balances also have to be attributed to the major rearrangement which I have made this year in staff organization and, particularly, committee structure for reviewing and planning, some of our target programs. I am convinced that this will result in a much more hard-hitting program, of a higher quality of science. We will get more for our dollar out of it later on but in the process of changing over, I think one inevitably does slow up the wheels a bit so that we are, this year, with a substantial amount of unobligated funds.

CANCER BUILDING

Mr. FOGARTY. You are requesting some new language in the bill. Why is this necessary?

Dr. ENDICOTT. The language in the bill, the new language, is simply to enable us to carry forward funds to complete the plans and specifications for the cancer building.

Mr. FOGARTY. When were the funds made available?

Dr. ENDICOTT. They were made available in 1961, sir.

Mr. FOGARTY. When will the plans and specifications be completed?

Dr. ENDICOTT. They should be completed, according to my information, early in the fall.

VIRUS-CANCER RESEARCH

Mr. FOGARTY. Last year, we urged you to increase your attention to virus-cancer research. What are you doing in that regard?

Dr. ENDICOTT. Well it has been a very exciting year in this field.

USE OF ANIMAL MODEL SYSTEMS

I might explain that over the past 6 or 8 years, there has been a gradual acceleration, particularly of research on animal model systems.

Mr. FOGARTY. Animal what?

Dr. ENDICOTT. Animal model systems, in which one can control variables quite precisely and work rather rapidly. These have mostly been in mice, and the work has particularly focused on viruses that cause leukemia in mice. Now, as a result of some beautiful studies in this field, many of them carried out by our own intramural staff under the leadership of Dr. Bryan, we have a situation in which, at least in the laboratory, we now have methods which rapidly permit you to demonstrate the causal relationship between the virus infection and the appearance of the leukemia, to recover the agent, to grow it in tissue culture, to grow it in large quantities, so that you can prepare immunizing vaccines or even produce it in sufficient quantities in the laboratory, so that you can make actual chemical studies on the virus itself.

Now, in the past months, we have applied the knowledge from this system or method that has been worked out with mice to patients in the clinic, and we are now moving along, I think, very nicely, studying the possible role of viruses in human cancer.

RECOVERY OF VIRUS FROM BLOOD SAMPLES

A field which the task force I mentioned has selected to concentrate on particularly is the possible role of viruses in the production of acute leukemia in children. With the techniques that have been worked out in the mouse and the rat, one can take samples of blood, put them in a centrifuge, get rid of the formed elements—the white cells and the red cells, and then spin down the more or less clear fluid and recover a little pellet in the bottom which is practically pure virus. This, as I say, was worked out in mice. When one examines this pellet under the electron microscope, he can identify virus particles in the pellet. We have been applying this in acute leukemia in children and a very substantial number of the children—not all of them—show rather large numbers of—if you will permit me to say so—virus particles in the pellet. At least, they look like the virus particles, which we get in mice.

We have learned a lot in the last year about the detailed structure of the mouse viruses and some of this detailed structure is also being seen in the material from the children.

Now, the problem at this point is always, well, are they really viruses, and do they really cause the disease?

In establishing a causative relationship, the next step is to try to get these things to grow in some other system, in an experimental animal, or in a tissue culture, and during recent months, we have had at least suggestive experiments which would indicate that we are getting some kind of replication of virus particles in some animals and also in some tissue cultures.

Now, the work at this stage requires repetition. There is quite a lot of work yet to be done, and our virologists, I am sure, would be the first to say we are a long way from having any uncontroverted proof, but I have a lot of confidence that this proof will be forthcoming.

We have decided to devote a major amount of our resources and energy to moving forward here, just as rapidly as possible.

Mr. FOGARTY. You started to say there were two other areas you are interested in.

Dr. ENDICOTT. In the virus field I wanted to mention several things that have happened in recent months which are important, we believe.

ADENOVIRUSES PRODUCE CANCER IN EXPERIMENTAL ANIMALS

Dr. Trentin, in Texas, and Dr. Huebner, at the National Institutes of Health, have demonstrated that two human viruses, two of the adenoviruses, produce cancer in experimental animals. In addition, in recent months, there has been shown that one of the monkey viruses which at times may contaminate vaccines grown in monkey cells, simian virus 40, produces cancer in experimental animals.

Now, we do not believe that at the present time there is any cause for alarm nor do we have any evidence that adenoviruses produce cancer in man.

But, certainly it is something which must be examined. So we have in collaboration with the Division of Biologic Standards and the Bureau of the Census vital statistics group mounted a rather elaborate

watch on selected segments of the population that may have been exposed at one time or another to the suspect viruses to see whether we can see anything in human populations.

CORRELATION OF VIRUS EXPOSURE TO CANCER INCIDENCE

At the present time, the early results would not indicate that the vaccines have had any effect on cancer rates. But it is becoming quite apparent that we are going to have to make a very careful and long-term correlation of human exposure to viruses as it relates to the incidence of cancer.

Now, this you can start at either end. You can begin with a cancer patient and analyze the antiviral antibodies that you find in the cancer patient and compare them with normal controls to see whether the cancer patient shows any evidence at that time of an abnormal virus experience or you can begin at the beginning and chart the virus experience of the developing individual and see whether you can correlate early virus infections with an appearance of cancer later on.

This is a tough one because even in the experimental animal which has a lifespan of, let us say, 2 years, the exposure to the virus which predetermines that the animal will get cancer may well occur in the first weeks of life.

At the time of the infection there may be some evidence of infection and you can find substantial numbers of viruses and so on.

Then to all intents and purposes, the virus goes away and you cannot detect it. Antibodies may or may not disappear and then, 15, 18 months later the animal develops cancer.

This is for an animal with a 2-year lifespan. When you think about a man with a 70-year lifespan, and the possibility that infection may occur in infancy while the cancer may not appear until age 60, the problem of the scientist to establish this relationship over this long timespan is a very difficult problem.

Now, we think it is very important to do it anyway, because at least in some of the virus cancers of the experimental animal one can prevent the cancer essentially by a vaccination procedure early in life, that is, exposing the animal to a vaccine of killed or attenuated virus.

I expect the serodiagnostic studies will develop rather rapidly when we obtain the resources. We are in the planning stage already, especially with regard to the prospective studies.

VIRUS STORAGE PROBLEMS

One thing it presents is a very large storage problem because the specimens collected from the people under observation have to be stored at low temperatures—way below zero, in liquid nitrogen or something of that sort, temperatures around 100° below zero over long periods of time.

The equipment is expensive and some of it has not even been developed yet and when you work with human populations and you are studying a specific kind of cancer, the population has to be rather large.

You may follow several hundred thousand people and, of course, the specimens pile up pretty fast that way.

We are coming along well in the planning stages. We have identified some population groups we want to work with.

We have some diagnostic reagents. A number of them are now in production. The virus theory is in a ferment right now in the cancer field.

LEVELING OFF OF RESEARCH GRANTS PROGRAM

Mr. FOGARTY. Your largest increase is \$4,088,000 for research grants, but as I look at the justifications, you are saying this is needed just to continue going projects and the same number of new projects as you are financing this year.

You are not budgeting any funds to enable you to increase the number of new projects.

Dr. ENDICOTT. This would provide for the same number of new projects as we have provided this year; yes, sir.

Mr. FOGARTY. In effect, this budget that is before us is aimed at leveling off the program.

If you have just sufficient funds to start the same number of new projects as you had the year previous, to me that is leveling off and I do not think the people of the country want to level off this program. I think they want you to expand research programs in this area.

Or am I wrong?

Dr. ENDICOTT. Well, sir, I suppose you are the better judge of that than I am. I think the projection for the research grant budgets this year was based on a different formula which does not crank in the expansion that has been used previously.

This does provide some increase, but it does not presuppose as much increase next year.

Mr. FOGARTY. There is no progress as I look at it. In new projects you have the same number in 1963 as you have in 1964.

Dr. ENDICOTT. Well, one starts new projects in part as a result of termination of old ones and one budgets in addition for new projects by bringing in additional funds.

Now, the program provides an increase for, first of all, indirect costs and it provides for a continuation of the supplemental requirements and it provides an estimated \$1,300,000 for noncompeting continuations in the programed chemotherapy area.

Mr. FOGARTY. And how many new grants in 1964?

Dr. ENDICOTT. There is no increase provided. It is to take care of 389 new grants, the same as 1963.

Mr. FOGARTY. So the answer to my original question is that there is no increase; no increase in the number of new grants.

Dr. ENDICOTT. Yes, sir; that is correct.

REDUCTIONS IN ORIGINAL REQUEST

Mr. FOGARTY. And also, your budget shows almost a \$10 million reduction from what you asked originally for your Institute. Do you think your original request of \$155 million was a good one?

Dr. ENDICOTT. Sir, my original request was—

Mr. FOGARTY. \$154,999,000 from the table that I have. Was that your original estimate?

Dr. ENDICOTT. The history is that my original estimate was for \$163 million.

The estimate to the Department of Health, Education, and Welfare was \$155 million and the Department's estimate to the Bureau of the Budget was \$145 million.

Mr. FOGARTY. You estimated a need for \$163 million, and this budget is \$145 million. That is a cut of more than \$18 million.

Dr. ENDICOTT. Yes, sir; that is correct.

Mr. FOGARTY. Now, one of the estimates that I have here was made on February 4, which is not long ago. In your professional judgment at that time you estimated a need for \$163,526,000; is that right?

Dr. ENDICOTT. That is correct.

Mr. FOGARTY. Do you still think that amount could be used efficiently and effectively?

SPECIALIZED RESEARCH FACILITIES

Dr. ENDICOTT. Well, sir, I would like to point out that this budget has something in there which is unusual so that it is not directly comparable.

Because I have suggested in this budget the needs for some "no year" money to get on with our contract activity.

If you took out the nonrecurring item that would be reduced to about 150.

Mr. FOGARTY. I do not know what you are talking about. I wish you would tell us a little more about that.

Dr. ENDICOTT. Yes, sir. I realize this is unusual. I was asked for a professional judgment so I gave it.

In the virus research we have an enormous problem of trying to contain these viruses, to keep them from spreading from animal to animal or from the animal to the investigator.

It appears, in order to do sound work, as though we may have to work in what is essentially a germ-free system. These resources do not exist. They are going to have to be created. The same thing is true in the studying of chemicals as the cause of cancer, particularly when one studies them in the atmosphere in low concentration over a long period of time with a large number of animals.

This requires precision control of the atmosphere and it also requires very careful removal of these chemicals from the exhaust in order to keep from contaminating the whole environment and this requires extensive air scrubbing equipment and so on.

The facilities do not exist anywhere. They are going to have to be created. This type of research requires an extensive amount of industrial know-how. We are certainly going to have to get industry into this picture in a major way.

I am unable to find concerns that are willing to advance the kind of capital we are talking about to build a new plant on the basis of a 1-year contract because obviously it requires a number of years to amortize this kind of investment and they are not able to go out and find the capital for it on the basis of 1-year contracts.

It is my feeling that our ability to cope with these particular areas is going to be substantially improved with some new device for solving the problem.

There are ways this could be accomplished, perhaps, by changing our enabling legislation. But it is also possible to do it under existing legislation, I believe, provided one had the "no year" fund to permit one to make a longer contract.

ADEQUACY OF THE BUDGET

The \$163 million budget which you referred to would be reduced to \$148 million if the \$15 million in no year money were excluded.

Mr. FOGARTY. Do you want to take it out?

Dr. ENDICOTT. I do not know—I suppose, this I want to emphasize, that this simply reflects my own personal opinion and does not take into account other needs.

Mr. FOGARTY. I asked you for your own opinion, that takes you off the spot so you can say what you really think.

Perhaps you think \$163 million is a very conservative estimate. Maybe it ought to be \$200 million.

Dr. ENDICOTT. I do not think it should.

It is always easier to guess at this time of year, of course, than earlier in the year. But I would like to say that I will—I am not suggesting that \$200 million would be better.

In fact, I am confident we could not properly program that kind of money.

Mr. FOGARTY. I am very disappointed in the budget that you are coming up with this year, especially in the research grant area where you are showing no increase in new projects over 1963. To me this is leveling off and perhaps could be construed in some areas as going downhill. I think we ought to be continuing that gradual increase in the area of research.

TRAINING AND FELLOWSHIP GRANTS

Now, you are requesting a relatively small increase of less than 10 percent for training and fellowships. Is this going to keep pace with the recommendations in last year's manpower report to the committee?

Dr. ENDICOTT. In answering that question, sir, I would like to draw your attention to something which has been developing over the past 3 or 4 years which I think is a very great force in future planning as far as the field of cancer is concerned.

This is one field of science which does not really identify with any particular discipline or specialty.

If you take—a fellow institute, for example, Institute of Neurology and Blindness, there are a number of clinical specialties and basic disciplines which are more or less exclusively concerned with those diseases.

In the field of cancer this does not exist. We use some of everything.

EMPHASIS ON BROAD-BASED TRAINING

Now, in the training of these individuals many of us believe—I would not say everyone—but many of us believe when you are training a biochemist you should give him broad training in biochemistry until he is thoroughly competent as a biochemist and only at that stage

should you attempt to bring about narrow specialization in the biochemistry of cancer.

Now, until a few years ago, the only training funds that were available were those that were available through the categorical institutes.

But as training funds have become available through the non-categorical program and as funds have become available increasingly to the institutions through the general research support grant, the departments of biochemistry, of physiology and so on have turned increasingly to noncategorical sources of funds for the support of the training up to the point where the man acquires general proficiency in his field.

I am convinced that the role of the Cancer Institute, for the long pull in the training of professional manpower, will really begin at the point where the man has completed his doctoral degree in the basic science or completed his clinical specialty training and is a thoroughly competent internist or biochemist or what have you, and then we will put the finishing touches on him.

So I would not anticipate that the increase in the Cancer Institute training programs would necessarily parallel those in these important general training programs which I think probably will meet our needs better than if we attempt to introduce a strong emphasis on the cancer early in the training.

Dr. SHANNON. I would like to comment on that.

Mr. FOGARTY. Before you comment, are you familiar with the recommendations of last year's manpower report?

Dr. ENDICOTT. Yes, sir.

Mr. FOGARTY. Do you disagree with the findings of that report as far as manpower is concerned as it would apply to your Institute?

Dr. ENDICOTT. No, sir, I do not.

But I believe—

Mr. FOGARTY. Is this budget going to keep pace with the recommendations in last year's manpower report to the committee?

Mr. KELLY. I do not believe there was a report by the Cancer Institute. There was only a report covering total medical research requirements.

Dr. SHANNON. That was one of the points that I wanted to bring out, Mr. Fogarty, if I may.

AREAS HAVING SHORTAGE OF PERSONNEL

As I look at the Cancer Institute's programing, I can envisage a shortage and really a critical shortage in personnel in perhaps four general areas.

As Dr. Endicott goes forward, particularly in the field of virology, more particularly in terms of purification of viral bodies, identification and fractionation and the like, he is going to find that his program is grossly short in the physical aspects of virology. It is because there are competing needs in other institutes in virology. In the general field of environmental science relating to the causation of cancer he will find himself grossly short in first rate pharmacologists, general toxicologists and in this he will be competing with the people who are trying to develop overall programs in environmental health and insofar as they push their programs, it will increase the shortages in cancer.

I think, furthermore, although he will find himself critically short of well-rounded clinical scientists who have a broad knowledge of modern concepts of clinical pharmacology and clinical trial, the point that he makes is certainly true.

We have come to appreciate this in the last 2 or 3 months. It is difficult for the Cancer Institute to structure a training program to satisfy the very needs that he requires.

Now, beginning in 1957 we developed a Division of General Medical Sciences and pulled a lot of the general training out of the various categorical institutes and localized at that point.

What we have not found the ability to do, and we faced up to this at that time, is to reflect in an adequate manner, either in program requirements or convincing arguments to our advisory groups or training groups, the Public Health Service and the Department, an estimate of these quite specific needs of the categorical institute within the overall program of the Division of General Medical Sciences for basic training.

One of the reasons why I think it has not been solved now is up to the present time we have had a council and an advisory structure and committee structure under that council, that addressed itself to all the problems in the Public Health Service.

I think by having our outside consultative groups now bear down on problems relative to NIH across the board we will get a thoughtful program development such as we have not had—such as was not possible in the general area at the present time.

DIFFICULTY IN FILLING KEY POSITIONS

I might say another difficulty that the Cancer Institute has found almost insurmountable in the past 6 to 8 months is the complete inability to replace certain key personnel.

I think, sir, that the Cancer Institute program has been suffering from that.

I point out that some 3 years ago we took Dr. Mider, who is now in charge of our laboratories and clinics, and last year we took Dr. Sessoms.

These are key people. Dr. Endicott is fortunate in that he has has been able to recruit Dr. Kotin from the west coast. He is the only senior person that the Cancer Institute has been able to recruit in the last 4 years.

Now, I think that you are beginning to see in the Cancer Institute, Mr. Fogarty, in its extramural program, what we are beginning to see in the direct operation.

You cannot have a far-reaching highly significant program in the absence of an adequate number of highly superior individuals to give leadership.

I think the program Dr. Endicott has at the present time reflects sharp appreciation that in the categorical areas, one must isolate certain problems and concentrate upon them and this is the reason he has been doing so well in certain of the areas.

But, one must also have in the top personnel echelons an adequate number of senior superior individuals if the program is to flourish, and I think the first time in the extramural area you see in the Cancer

Institute today—you are beginning to see the deficiencies that come from an inadequate personnel system.

ADEQUACY OF BUDGET REQUEST

Mr. FOGARTY. In view of that, do you think we should cut the appropriations to the NIH?

Dr. SHANNON. In the 1964 request? I mean the overall amount? In the long range, unless the senior personnel system is satisfied as to need, I think a shortage of key personnel will automatically put a limit on the growth.

Mr. FOGARTY. Do you think this budget ought to be cut?

Dr. SHANNON. No, sir. I think Dr. Endicott can handle what he has.

But he cannot do some of the things that were implied in your question, that is, play his role and satisfy the personnel shortage, looking forward to a decade from now. I do not think he has the senior professional personnel to do the job that is required in that area.

ORIGINAL REQUEST FOR TRAINING AND FELLOWSHIPS

Mr. FOGARTY. How did your request for funds for training and fellowships compare with the allowances by the Bureau of the Budget?

Dr. ENDICOTT. This is a very interesting situation. Originally, the estimate which I gave to Dr. Shannon provided for \$6 million in fellowships and \$15 million in training. That budget estimate was prepared last spring. The budget estimate which we were invited to submit as our own personal judgment which was prepared in January of this year requested \$4 million in fellowships and \$8,900,000 in training.

Now, we have been making a very intensive analysis of our programs and of the programs of the other Institutes in the General Medical Sciences, the Atomic Energy Commission, the American Cancer Society, and we have had an opportunity to look very closely at the quantity and quality of proposals which we have been receiving from the universities and, as you can see, I have had to revise my estimates way down as to what I think we probably can profitably utilize. But I would like to make this one point, because it is easy to overlook in this numbers business, what is really going on.

RADIOBIOLOGY TRAINING

The areas which we have identified as critical shortage areas have also been identified as critical shortage areas by the Institute of General Medical Sciences and some of the other organizations and a good case in point is the field of radiobiology.

During the time when we were discussing the present estimates with Dr. Shannon he requested that I look into the field of radiation biology very carefully to determine whether the Cancer Institute should have an intensive program in this field.

We did so. This area overlaps obviously with the Atomic Energy Commission, which is launching a major program in the field.

It is of interest to the Division of Radiological Health and it has been of particular interest to the Institute of General Medical Sciences.

We found that there was in being a training support program which we believe was adequate to take maximum advantage of the training opportunities which now exist in the academic institutions and after very careful study, I recommended to Dr. Shannon that the Cancer Institute not undertake such a program.

This recommendation was accepted. Now, there is a program of training, a good program of training. It is in being, it is moving, and for us to launch a new one, I think would not add anything, sir.

COMPARISON WITH MENTAL HEALTH BUDGET

Mr. FOGARTY. How does the Mental Health Institute do so much better than you?

Dr. ENDICOTT. Well, I am not prepared to admit that they do, sir.

Mr. FOGARTY. Well, they have considerably more new research grants budgeted for 1964 than in 1963.

Dr. ENDICOTT. Well, sir—

Mr. FOGARTY. In dollars it is almost double.

Dr. ENDICOTT. In research?

Mr. FOGARTY. Yes; for new research grants.

They seem to be doing better than you. I'm all for it, but I think your Institute should, too. They are better off in training than this budget of yours, also.

DIFFERENCE IN AIMS OF MENTAL HEALTH AND CANCER TRAINING PROGRAMS

Dr. ENDICOTT. I would like to comment on the training aspects, at least. There is a very substantial difference between the objectives of the Mental Health Institute and the Cancer Institute in the training area.

The Mental Health Institute is undertaking broadly to make up for an enormous deficiency of certain types of medical and ancillary personnel necessary to purvey services to the mentally ill. This, then, deals with large numbers of different kinds of people—the psychiatrist, nurses, social workers, and so on.

Our training program is not beamed toward the training of people to purvey services, but to train investigators and trainers of investigators which is a much smaller enterprise.

Now, there has been a transfer of one of our functions from the Cancer Institute to the Bureau of State Services. This is the general area of cancer control and this program is launching a new training program for making up for deficiencies of doctors specially trained in the management of cancer.

Now, these kinds of people will work in large medical centers and be in effect consulting surgeons, radiologists, and so on, who serve a very large population and to whom difficult cases are referred.

But the treatment of a cancer patient is the responsibility of the entire medical profession, including Dr. Felix's psychiatrists. Cancer patients have a great deal of trouble adjusting to the disease and so do their families.

But we cannot identify this kind of doctor or that kind of doctor or another kind of doctor, because they are all involved in the management of cancer patients in one way or another and this problem, the problem of getting enough doctors, is something which the Cancer Institute certainly cannot handle.

This is a problem for an entirely different order of magnitude of programing which has been proposed for legislation.

This really deals with the question of the whole problem of medical education and total number of doctors. With apologies to you, sir, I think we just have a different kind of problem than Dr. Felix in that we are not the right organizational unit to make up these general deficiencies which certainly exist.

Mr. FOGARTY. Well, let us get back to the statement I made. This increase of about 10 percent for your training program is a very conservative increase as I see it.

Dr. ENDICOTT. Yes, sir.

Mr. FOGARTY. Do you plan any shifts in emphasis next year?

RESEARCH INTO INTERACTION OF VIRUSES, CHEMICALS, AND RADIATION

Dr. ENDICOTT. We have already set into motion some activities which will certainly result in internal shifts. I have mentioned one of them. This is in the field of virology. Another one is in the field of interaction of viruses, chemicals, and radiation.

We are starting up a program in collaboration with the Atomic Energy Commission this year which I expect to grow to very substantial proportions.

This is a program to be carried out at Oak Ridge in collaboration with AEC, investigating viruses, radiation, and chemicals together as causes of cancer.

However, we are in a startup period this year. We have a relatively small amount of program going, and we are getting facilities renovated and getting ready to go.

Next year we will be in a buildup phase. This will certainly represent substantial shifts. Now, we are also reprograming to a considerable extent in the chemotherapy area, because it now appears that we have a pretty good laboratory model for detecting drugs which are effective against acute leukemia.

NEW DRUGS FOR LEUKEMIA

Mr. DENTON. Against what?

Dr. ENDICOTT. Acute leukemia in man. Over the past 12 to 24 months we have had 3 excellent new drugs which have a high degree of activity in human leukemia.

That is the first hit we have had in years, I suppose. So we are dedicating to the specific search for antileukemia drugs—

Mr. FOGARTY. When you say "we," whom do you mean?

Dr. ENDICOTT. I was using "we" collectively for the Cancer Institute, including grantees and contractors.

What this amounts to is that a substantial number of contractors who have been engaging in general screening, using a variety of methods, will now switch over specifically in this area.

Mr. FOGARTY. Give us a more detailed statement for the record, and point out the part that the Institute played.

(The information follows:)

THREE ANTILEUKEMIC AGENTS DEVELOPED, IN PART, THROUGH THE NATIONAL CANCER INSTITUTE'S CHEMOTHERAPY PROGRAM

At the present time there are six different classes of chemical materials capable of producing complete remissions for varying lengths of time in a certain percent of patients with acute leukemia. From a therapeutic and morphologic standpoint, specific differences are found when the disease afflicts adults or children. In general, childhood acute leukemia compared to the same disease in adults is more responsive to therapy, and primarily of the lymphocytic variety. In adults, acute leukemia is predominantly of the myelocytic type. Those compounds which are representative of the classes of chemicals mentioned and which are currently the compounds in use, are prednisone (hormone corticoid), 6-Mercaptopurine (purine antagonist), Amethopterin (folic acid antagonist), Cytosan (alkylating agent), Vincristine (plant product), and Methylglyoxal-bisguanyldrazone. The former three of these compounds were in use prior to the initiation of the national drug development program for cancer. The latter three were synthesized or isolated in the recent past years and the Cancer Chemotherapy National Service Center program has played, and continues to play, a vital role in their development. The first five compounds, as listed, are effective against childhood acute leukemia. The sixth compound is of primary value at present because it is predominantly the agent for the treatment of adult acute leukemia.

METHYLGLYOXAL-BIS-GUANYLDRAZONE

This compound was first synthesized by Friedlander and French in 1958. It was found to have antitumor activity against mouse leukemia L-1210. The chemical was thoroughly evaluated in the preclinical program of the CCNSC and placed in clinical trial in the cooperative group program which is part of the CCNSC and supported by grant funds provided by the NCI. Subsequent studies indicated that the compound had distinct activity against adult acute myelocytic leukemia for which previous therapy had offered little. According to recent figures, the best therapy, exclusive of Methylglyoxal-bisguanyldrazone, produced complete remissions in approximately 10 to 13 percent of all adults afflicted with this disease. The most recent data from studies with Methylglyoxal-bisguanyldrazone indicate that the compound is capable of producing complete remissions in as high as 55 percent of adults with acute leukemia. This compound does not show significant activity, however, against childhood lymphocytic leukemia. Further studies are in progress in the CCNSC clinical program in an effort to determine the optimum manner in which this compound should be administered, as well as in exploring its possibilities for therapy of other hematologic malignancies and in the treatment of patients with more common solid tumors.

CYTOSAN

Cytosan (cyclophosphamide) is one of the compounds classified as alkylating agents. This compound was first synthesized in Germany; brought to this country and now distributed by the Mead Johnson & Co. It was evaluated and screened thoroughly in the preclinical program of the CCNSC and found to have extensive activity in animal tumor systems. Thereafter, in collaboration with the Mead Johnson & Co., the compound was thoroughly studied in several of the cooperative clinical groups which are a part of the CCNSC. In general, Cytosan has been found to have activity against those human malignancies for which alkylating agents are effective to varying degrees. In acute leukemia, however, it has been unique in that it is the only alkylating agent to date which has been found to be useful. The most recent information indicates that Cytosan is capable of producing complete remissions in approximately 18 percent of all children with acute lymphocytic leukemia, and partial remission in 11 percent more. Of distinct value is the fact that Cytosan will produce remissions in patients who have become resistant to other drug therapy. In addition to acute leukemia, Cytosan has been found to produce measurable response in patients with the malignancy, multiple myeloma, a very resistant disease to therapy.

VINCRISTINE

Vincristine is derived from the plant, periwinkle, and was developed entirely through the efforts of the Eli Lilly Co. This compound has been studied extensively by members of the CCNSC cooperative group clinical program, receiving financial support from the National Cancer Institute. The compound has been shown to produce complete remissions in as high as 55 percent of children with acute lymphocytic leukemia and partial response in 13 percent more. The average duration of complete remission in general is short, however, being approximately 9 weeks as compared to that for Cytosan of 29 weeks; 6-Mercaptopurine of 21 weeks, and Amethopterin of 17 weeks.

ESTABLISHMENT OF A VIRUS AS AN ETIOLOGIC AGENT

Dr. ENDICOTT. Now, other shifts in emphasis are probably going to occur back and forth from diagnosis, treatment and prevention as things move along in the virus field.

This is one thing that I would like the committee to appreciate.

The establishment of a virus as an etiologic agent provides an opportunity for prevention if you can eliminate the thing or immunize against it.

It also presents opportunities for diagnosis since it may produce detectible antibodies that are circulating in the blood.

It also may present an opportunity for therapy. We are presently doing virology in the chemotherapy area, specifically looking for antiviral drugs. These shifts can occur quite rapidly. I have mentioned a few. There may well be others by this time next year.

SIMILARITY TO SALK VACCINE DEVELOPMENT

Mr. FOGARTY. Could this approach be comparable to the development of the Salk vaccine?

Dr. ENDICOTT. It could be, sir.

Mr. FOGARTY. They went through some of the same steps, did they not, that you are going through now?

You do not know when the breakthrough may come, if you want to call it that.

As I remember the progress in this area, Dr. Salk went through some of these same steps that you just talked about.

Dr. ENDICOTT. I hope that this may be so.

Mr. FOGARTY. As a layman it looks to me like it is far from a sure thing but it could be possible? I am looking for some comparisons to make if I can.

Dr. SHANNON. I can give the steps and if you want them on the record. In the last, in the late 1940's the first step, subsequent to identification of virus was the demonstration of polio infection and was due to the three types of specific virologic agents each with different immunological characteristics. The second break was the demonstration of the ability to grow the tissue culture.

The third step was the ability to grow in a tissue culture in such quantities as to make harvesting feasible and the fourth step was the ability to inactivate in the absence of destroying the immune characteristics of the material.

Now, those were four discrete steps.

Mr. FOGARTY. Supply for the record that comparison.

(The information follows:)

COMPARISON OF THE POLIO STORY WITH DEVELOPING CANCER VIRUS RESEARCH

Prior to the intensive attack on polio initiated in the early 1930's under the sponsorship of the National Foundation for Infantile Paralysis and supported by the March of Dimes program, progress in the field was determined by the interests and efforts of a few scientific groups or individual scientists. Poliomyelitis had already been found to be caused by a virus, of which there were several different antigenic types. The virus was highly specific for humans, but had been found to multiply and to produce typical clinical disease in certain non-human primates, particularly rhesus monkeys. Smaller and less expensive test animals of other species were not susceptible to the virus and therefore could not be used. Monkeys were highly expensive as compared with smaller experimental animals such as were usually employed in laboratory research. Furthermore a relatively long period of time (several weeks or more, depending on quantity of virus) was required for the monkeys to develop polio after experimental inoculations. Even more important was the fact that only very small quantities of virus could be recovered from each highly expensive monkey; sufficient viral antigen could not therefore be produced under economically feasible conditions to support adequate research on vaccines, much less the commercial production of vaccine for widespread human use.

During the pre-March of Dimes period the money available for medical research was not sufficient for more investigators to think in terms of using monkeys as test animals in the numbers that would be required in any systematic intensive attack on the problem. Attention was therefore directed toward a search for a small laboratory animal that would be susceptible to the human polio viruses, and systematic laboratory studies were confined to "animal-model systems" such as the Theiler virus of mice, which is specific for this species, but which produces symptoms in mice somewhat comparable to polio in humans. However, monkeys were used in limited number for attempts to obtain answers to the most crucial questions, such as, Is polio virus present in excreta of infected humans, etc.?

With the availability of adequate funds and the attraction to the problem of large numbers of highly qualified investigators, solutions to the problems began to come. Expensive monkeys could now be used as "biological indicators," simply to determine whether polio virus was present in the feces, urine, and saliva of humans suffering from polio. It was essential to know how the virus was spread in nature. Since the quantities of virus transmitted in nature may be relatively low, several monkeys were required for testing each specimen from each patient, and many patients had to be studied. A similar use of monkeys was required to determine whether flies or other insects could be carriers or vectors of the virus.

Twenty years of intensive effort using primates as test animals resulted in the discovery of many strains of polio virus and in a fairly thorough understanding of how the disease was spread, but the relatively small yield of virus from each expensive monkey still precluded the production of viral antigen for use as vaccine. The number of monkeys in the world was simply not sufficient for the production required.

The next break came with the development of tissue culture technology (i.e., the growth of animal tissue cells in test tubes), coupled with the advent of antibiotics. Before antibiotics, cells growing in test tubes could not be used for searching for viruses in specimens such as saliva, urine, and feces, because these contained many bacteria which grew rapidly and killed the cells. Antibiotics kill bacteria, but do not inactivate viruses. Specimens treated with antibiotics could therefore be added to cells in tissue culture for the growth of any virus that might be present. The advances in tissue culture technology which permitted the growth of almost unlimited numbers of individual test tube cultures under practical conditions was an equally important factor in breaking the polio problem. Incidentally, a major number of the basic steps and discoveries which permitted this development took place at the National Cancer Institute and resulted from moneys appropriated for cancer research. The National Cancer Institute had placed one of the highest priorities on the study of normal and cancer cells in controllable tissue culture systems. The polio problem therefore profited by cancer research developments, and, as will be mentioned in more detail later, cancer

research is now profiting from the tremendous contribution to biological research made in the course of solving the polio problem.

With the availability of tissue culture units instead of whole animals, the routine testing in large numbers of samples that goes with any systematic study could be stepped up by many orders of magnitude. For example, seed quantities of susceptible cells from one monkey could be dispersed among, and grown out into full cultures in, hundreds of separate test tubes, each of which had the same power of detecting the presence of polio virus in a given sample, even more efficiently than an entire monkey had done previously. This massive increase in testing ability not only increased by many orders of magnitude the numbers of patients and specimens that could be studied, but also permitted basic research under quantitative conditions which was essential for the next step in the war on polio; namely, the finding of a cell type which would support the reproduction of polio virus to the extent needed for the large-scale production of virus to be used as antigen for vaccination of large populations. The discovery that kidney cells of rhesus monkeys accomplished this purpose won the Nobel Prize for Dr. John Enders, and led to the production of a practical killed vaccine by Dr. Jonas Salk and a practical attenuated live vaccine by Dr. Albert Sabin and others.

Although the nature of the disease poliomyelitis—namely, that it was caused by a virus—was known at the time intensive efforts to bring it under control were launched, it took about 20 years to progress to the point of developing a satisfactory vaccine, and another 5 years to evaluate the efficacy of the vaccine. In attempting to draw a parallel between the successive steps in the solution of the polio problem and current research on the causation of human cancer by viruses, it should be strongly emphasized that no human cancer has yet been demonstrated to be caused by a virus. The first step in the human cancer virus problem—namely, the demonstration that at least one type of human cancer is caused by a virus—has therefore not yet been successfully made.

Since an increased effort on the cancer problem was launched only a few years after the polio program, why does cancer research lag so far behind the polio problem, and why hasn't this first step been accomplished? More appropriately, why do we think there is a virus associated with human cancer, and why is an intensive effort now being made to determine this?

When the increase in cancer research was launched by the Cancer Act of 1937 cancer was considered as a "mystery disease" the basic cause or causes of which were entirely unknown. Viruses were not even in the running at this time as factors to be seriously considered as causative agents. Because of its almost completely unknown status cancer was not attacked on the same scale as polio. The problem was not ready for this type of effort. Instead, an Institute was established to conduct research and to administer grants programs providing support for investigators in other institutions who submitted sound proposals for research on the problem. For many years the only tangible approaches to laboratory research were along the lines of (1) cancer induction by chemicals, and (2) increases in cancer in animal populations through genetic manipulation. A few chemical substances had been found to be capable of causing cancers in animals and since they possess certain structural similarities to known normal body chemicals (e.g., steroid hormones and certain constituents of bile), it was thought that cancer might be a metabolic disease caused by variations in the normal chemical constituents. Many years of effort along these lines led to the discovery of several hundred different chemicals that are capable of causing cancer. Many different structural forms were also represented. This led to the conviction that cancer was some sort of a general cellular and tissue reaction rather than a single specific disease entity, particularly a specific metabolic disease. This conclusion has been confirmed by later developments along several other lines, including studies in the clinic, and cancer is now known to be a complex group of many different diseases. Analogously, polio is only one of the many diseases in which paralysis of muscles occurs, and paralysis in itself is not a specific disease entity. Paralysis may be caused by many different viruses as well as agents of other types, including chemical compounds which act selectively on certain parts of the nervous system.

The genetic approach to cancer had developed from the success of geneticists in producing "high" and "low" cancer strains of mice through selective inbreeding. Three types of cancer were represented: breast cancer, leukemia, and lung tumors. The concept gained prominence that cancer was a disease involving the

hereditary mechanism. Intensive efforts to prove this for breast cancer of mice yielded results which indicated that the factor transmitted from parents to offspring did not follow known genetic laws and was not transmitted equally by male and female parent. Instead the hereditary factor was transmitted extrachromosomally primarily by the mother. Further studies proved the factor to be transmitted through the mother's milk and to have physical and chemical properties similar to the viruses known at that time. However, except for a few viruses associated with cancers in chickens (but which were not accepted as true cancers by leading pathologists of the time), all of the known animal viruses were associated with contagious infectious diseases. Since experience of modern scientific medical history had indicated that cancer was neither contagious nor infectious, the factor in milk of mice responsible for the transmission of breast cancer was at first considered as something other than a virus. Extensive additional investigations have yielded a similar viral-type agent associated with the hereditary leukemia of mice. All studies on these two agents have confirmed the fact that they are indeed viruses, and, although they cannot be distinguished from other viruses in chemical and physical properties, they do have certain different biological properties. Characteristically they must enter their new host very early in life or shortly after birth in order to be effective in causing cancer. But the cancerous disease does not develop until the animals reach middle or old age. The genetic approach, which involved observation of test animals throughout their entire life spans, had brought to light a new and subtle type of virus not previously known.

Important developments since the early 1950's in techniques of working with these subtle cancer viruses have led to the discovery of many new cancer viruses of mammals, particularly mice which have been most extensively studied. As in the case of polio of humans, several antigenically different leukemia viruses have now been found which produce the same manifestations of disease in mice. It is evident, therefore, that in the complex of diseases which we call cancer there are some specific disease entities, comparable to polio, which are caused by specific viruses, or by related viruses of a common family group. This is now known to be true for the leukemias of both fowls and mice. Since basic biological phenomena are not confined to narrow genetic types, but cut across broad species barriers, it is logical to expect that leukemias of other species may also be caused by viruses, including some of the leukemias of man. The same possibility holds for cancers of other types involving solid tissues, for which counterparts in laboratory animals have been found to be caused by viruses. If this be the case, then the possibility also exists of bringing a large segment, if not a major portion, of the cancer problem under control by vaccination or other preventive methods now known to medical science.

In addition to the logical expectancy based on the increasing discoveries of viruses associated with cancers of animals, indirect evidence has been obtained for a possible association of viruses with human cancer: (1) Studies under the electron microscope have revealed virus-like particles in a few cases of human leukemia resembling those which cause leukemia in chickens and in mice. However, proof that they are actually viruses and are associated with the causation of human leukemia has not yet been achieved. (2) Two recently discovered human viruses which may produce only mild respiratory disease in a few persons and may remain latent in many individuals throughout their lives without causing any manifestations of disease, have been found to induce cancers in hamsters when administered under certain artificial laboratory conditions. Proof has not yet been obtained that these viruses will cause cancer when given under conditions of natural transmission, or that they will cause cancer of man and other primates under the artificial conditions.

The slow progress in getting on with the human cancer virus problem is due to factors comparable to, but much more difficult than those encountered during the early days of polio research. Like polio viruses, the known cancer viruses are species specific and will "take" in other animals only of closely related species. The production of cancers in hamsters mentioned above appears to be an exception to this rule, but the situation is in some ways a dead end one since virus cannot be recovered from cancerous or other tissues or specimens of the hamsters later than a few days following inoculation.

An intensive search is now being made in laboratories all over the world for susceptible small animals which will reveal the presence and allow the systematic study of presumed viruses from human cancers. Various species of nonhuman primates are also being investigated in a few major cancer research centers,

but, because of the high cost, only on a limited scale; that is, such animals are not used in any general testing program but only for further study of selected specimens that have given some sort of suspect reaction by indirect methods of approach.

It is possible that, like the polio viruses, some human cancer viruses may become identifiable by their ability to propagate and produce characteristic lesions in monkeys or other subhuman primates. However, the length of the latent periods preceding detectable lesions cannot be predicted, and if they are very prolonged, e.g., many years, progress even with this lucky break could be quite slow. Judging from the age incidence of cancers of humans, those caused by viruses must have prolonged latent periods extending over many years if the viral agent must enter early in life in order to produce its effect, as do most of the known cancer viruses of animals. If other primates approach the human in this protracted period before cancers develop after infection with virus, the use of primates as biological indicators in large-scale systematic studies will be impractical. However, since human volunteers should not be directly used for establishing a causative relationship between suspect virus and cancerous disease, primates will need to be used with the hope that some species will be susceptible, and the long latent period will have to be waited out, whatever its length might be.

In view of the breakthrough on the polio problem brought about by tissue culture methods, why has the cancer-virus problem not moved as rapidly using tissue culture methods, and why has the difficult animal testing program not been circumvented, as in the case of polio?

In the first place, the polio viruses, as well as many new viruses that came to light with tissue culture methods, can be readily detected in a span of a few days to 1 week because generally they kill the cells as they multiply in them in the tissue culture units. The dead cells are biological indicators of the presence of the virus. Furthermore, the time required to kill and the lowest concentrations that kill can be used to make quantitative determinations of the actual amounts of virus that were present in the original specimens. This is not true for the cancer viruses. Most of the known cancer viruses of animals cannot yet be grown in tissue culture, and, of those that can, only a few produce changes in cells that can be recognized visually or under the ordinary light microscope. Those few cancer viruses that do produce characteristic changes which can be associated with virus infection did not do so at first, apparently as a result of the weak concentration of virus present in original spontaneous animal cancers. They first had to be passed through many generations of animal transmissions in order to step up the potency and virulence of the virus. In other words, the tissue culture methods used so successfully in polio research are not sensitive enough to pick up and amplify the small quantities of the more fastidious cancer viruses that are present in the natural diseases, even in the case of animal cancers known to be caused by viruses. To reemphasize; no cancer virus has yet been picked up or revealed for the first time in a tissue culture system, even in known animal virus cancers.

In those cases in which "souped up" animal cancer viruses can be grown in tissue culture, but produce no visible (light microscopic) evidence of their presence, the only direct method of detection at present is by inoculating filtrates of the tissue cultures into test animals of the same species. Indirect evidence can also be obtained by examination of the cells or culture fluids under the electron microscope or by interference of virus growth by the presence of another virus.

In studies on the human disease, animals of the same species cannot be used for detecting virus that might be growing in tissue culture but producing no observable effect. The indirect method of electron microscopy is therefore the only feasible method of monitoring tissue cultures at the present time. When virus-like particles are observed, aliquots of the cultures are injected into monkeys in a program now underway at the National Cancer Institute, but positive results have not yet been obtained in experiments that have been underway as long as 10 months.

Electron microscopes are expensive instruments which require a full-time professional and a full-time assistant to operate and interpret results. Because of the extremely small size and low density of the particles that must be sought out and resolved with impeccable precision techniques, only a few specimens can be adequately studied in the course of a day. One instrument and complement of workers could not begin to monitor all of the tissue culture units involved in

the search for cancer viruses by a single research virologist. Other criteria of determining the presence of subtle cancer viruses in animal tissue culture preparations are therefore being vigorously pursued. In the meantime, as much electron microscopic research as is available is being directed toward the study of selected human materials screened out by other indirect methods.

Another approach to the demonstration of possible human cancer viruses is through seroepidemiological studies rather than by strictly laboratory investigations. This involves the case study of literally hundreds of thousands of human subjects as well as laboratory testing of blood and other specimens in search of known viruses, such as those which cause cancers in hamsters or their telltale antibodies. A repeatable high correlation between the presence of virus—particularly early in life—and the occurrence of cancers of a particular type—even though later in life—would pinpoint for further investigation viruses which might be associated with cancer among the hundreds of human orphan viruses now known, but which have not yet been associated with any known disease. This is a formidable and extremely expensive undertaking which would extend over a long period of time, even a generation or more. Consequently, it is now being considered or projected only on a limited pilot scale. Research of this magnitude eventually will likely need to be done because cancer is now known to be a general type of reaction that can be brought about by many different types of viruses. Even common infectious viruses, such as influenza and vaccinia viruses, although not cancer-causing under usual conditions, may, in combination with known cancer-producing chemical lead to cancer production even though the chemicals were used in amounts smaller than would be effective in producing cancer without the participation of the virus. Such effects have been observed in mice. Finally, even if viruses associated with specific cancerous diseases are identified and propagated in the laboratory, proof of their association with human cancers will need to be obtained through long-term epidemiological studies, including tests on specimens banked early in the lives of individuals, for, ruling out the use of human subjects as test animals, no other method is now in sight of making the final crucial association between agent and disease.

CHEMOTHERAPY PROGRAM

Mr. FOGARTY. What progress are you making with your collaborative studies. I notice there is very little increase in funds requested and no more personnel.

Dr. ENDICOTT. This is an area by agreement with Dr. Shannon—

Mr. FOGARTY. Is he holding you back?

Dr. ENDICOTT. We are in essential agreement about this. The general level of the drug screening program we believe is about what it ought to be.

Mr. FOGARTY. We will place the special report on the cancer chemotherapy program in the record.

(The report follows:)

SPECIAL REPORT ON CANCER CHEMOTHERAPY PROGRAM

The nationwide cooperative cancer chemotherapy research program was established 7 years ago in recognition of a need to accelerate the search for effective anticancer drugs. Originally, the program incorporated screening and secondary evaluation of new substances and clinical trials of those that seemed to offer promise of efficacy in the treatment of cancer patients. Through these activities, it has helped stimulate the development of new concepts and techniques and has contributed in many ways to a general improvement in the care of cancer patients.

Now, the program has been broadened to include investigations of a number of other promising experimental approaches to drug treatment for cancer. In addition, the National Cancer Institute, which administers the program, has taken the lead in launching an intensive effort to extend the progress already made in drug treatment and supportive therapy for patients with acute leukemia.

THE PROBLEM

This year about 280,000 men, women, and children in this country will die of cancer. Though surgery and radiation therapy will save the lives of many, they are of little use in cases in which the malignant disease has become widely disseminated in the patient. Thus, there is an acute need for drugs that will either kill cancer cells or by some mechanism make it impossible for them to survive and multiply.

Because cancer is a large group of diseases, rather than a single disorder, many drugs will be needed. About two dozen are now considered useful in the treatment of various forms of cancer.

Thanks to drug treatment, several women who had choriocarcinoma and related tumors have been restored to good health even though their disease was far advanced. Tumors of this type are rare, however, and the drugs that suppress them came into use in other ways. Thus, this experience has provided no conceptual basis for chemical control of other cancers.

A number of other forms of cancer, especially the leukemias and lymphomas, can be arrested temporarily with drugs, resulting in prolonged survival for many patients. There has been a fourfold increase since 1947 in the median survival time of children who have acute leukemia, and enough knowledge has been accumulated to afford opportunities for additional gains.

On the other hand, drug treatment is only occasionally beneficial for many common types of malignant disease, including cancers of the lung, colon and rectum, and pancreas. On the whole, a promising start has been made, but much remains to be done.

THE PROGRAM

For the current (1963) fiscal year, \$33,015,000 of the National Cancer Institute's appropriation is earmarked for the chemotherapy program. The largest share, more than \$26 million, is allocated for contracts covering purchases of resources such as animals and drugs and services such as screening and statistical evaluation of clinical results. Of the remainder, \$4,300,000 is for grants to support cooperative clinical investigations and \$1,721,000 for administrative costs.

The program was formally divided into two segments during 1962. Screening and other preclinical activities remained within the Cancer Chemotherapy National Service Center, but the Clinical Branch was made a separate organization responsible for clinical investigations.

On the research level, several changes were made that will have a profound effect on the program in the years to come. Expansion of the screen, in accordance with longstanding plans, was completed. Instead of only 3 tumors in mice, about 20 in mice, rats, and hamsters are now being used. Though it is not possible to test every new substance in every tumor, the expanded, more flexible screen hopefully will pick out drugs useful not only in the leukemias and lymphomas, but also in the more common solid tumors. That it will actually do so will take 3 to 5 years to ascertain.

In the meantime, the number of substances to be screened annually has been reduced to keep the cost of screening more or less constant despite the increased expense resulting from the use of rats and hamsters. Plans for the current year call for screening of 6,000 synthetics, and 8,000 antibiotics plus plant extracts, which are being tested in increasing numbers in view of encouraging results already achieved with a few such substances.

Over the last 7 years, more than 70,000 synthetic chemicals and 100,000 natural products, mostly antibiotic filtrates, have been screened. A number of substances having some degree of usefulness have been found, including representatives of classes of compounds not previously known to have anticancer activity. These leads are constantly pursued in hopes of synthesizing closely related, but more effective, compounds.

At the same time, steps are being taken to explore other methods of uncovering new and better drugs and increasing the effectiveness of those already in use. To this end, biochemical studies of human tumors were begun during 1962. Tumor specimens are being collected and studied to obtain information about the enzymes they contain. It is hoped that such information, coupled with knowledge of how anticancer drugs work (another problem on which research is currently focused) will make it possible, on one hand, to design new compounds that will take advantage of biochemical defects in human tumors, and, on the other, to devise methods for studying one tumor at a

time to determine which drugs are most likely to provide effective treatment for individual patients.

Another approach being explored is the use of combinations of drugs, either simultaneously or in sequence, which is widely believed to offer a promising way of overcoming the problem of progressive, acquired resistance of tumors to single drugs. A model laboratory system has been devised for use in selecting combinations that prolong the survival of tumor-bearing animals without increased toxicity. Several such combinations have already been identified, but much additional research will be necessary before any clinical trials can begin.

Though research within the program has been focused principally on cytotoxic drugs (e.g., alkylating agents, antimetabolites) and hormones, the possible value of compounds that are not, in a strict sense, anticancer drugs has been recognized. Accordingly, preliminary work leading toward a search for useful compounds in two categories—radiation modifiers and antiviral drugs—was begun in 1962.

Two types of radiation-modifying chemicals are of interest. One would protect normal tissue while leaving cancerous tissues susceptible to the effects of radiation. The other would concentrate in cancerous tissue and enhance its sensitivity to radiation. Through the program, an effort has been initiated to develop suitable animal and tissue culture screening systems for use in identifying radiation modifiers. Actual screening will not begin until such systems are available.

Interest in viral chemotherapy has been stimulated in part by mounting indications that viruses may cause some forms of human cancer. In addition, both cancer in its various forms and known virus-caused diseases are now widely assumed to involve synthesis of abnormal nucleic acids within living tissue, which may mean that drugs effective in one group of diseases will also be effective in the other.

For the time being, the viral chemotherapy studies within the program are also directed toward the development of test procedures, as well as toward gaining an understanding of the mechanism of action of the few compounds now known to have some antiviral effect. Viruses known to produce tumors in animals as well as those not known to do so will be utilized in wide-ranging investigations of various aspects of viral diseases and the agents that cause them.

Clinical activities within the program moved ahead rapidly during 1962. Trials of 17 new nonhormonal drugs were begun, and an equal number of hormonal compounds, almost all of which were developed under the auspices of the program, were placed in trials by the cooperative breast cancer group. Thus, the number of investigations begun since the program was set up reached 378, of which 120 were completed by the end of the year. Some 27,000 patients have been involved.

Most of the initial studies of drug treatment in conjunction with surgery, which exemplify the kinds of projects that the program is uniquely equipped to undertake, have been completed except for followup of the patients treated, and several others will be initiated in the months to come. Though the results have not been uniformly good, the concept of combined treatment remains highly attractive. In the hope of obtaining better results, only drugs that have been shown to produce a favorable response in at least 15 percent of patients having advanced cancer of the types to be studied will be utilized in future surgery-adjutant investigations.

Recently, steps were taken to speed up trials of new drugs, particularly broad spectrum studies in which drugs are tested in patients with various forms of cancer. Formerly conducted by one group at a time, such trials will, in the future, be carried on simultaneously by regional medical and surgical groups. One group of each type is in operation in the eastern, central, and western regions of the country.

In all, 24 cooperative groups comprising more than 700 investigators are now working in the program which makes communication somewhat difficult. To remedy this, negotiations have been initiated to place a physician of the Public Health Service commissioned corps with the chairman of each cooperative clinical group, with responsibility for analyzing and interpreting data to the National Cancer Institute on a day-to-day basis.

THE ACUTE LEUKEMIA TASK FORCE

A series of profound and extremely heartening advances has been made over the last 15 years in drug treatment and supportive therapy for patients with leukemia, particularly acute leukemia. Briefly, they include the introduction of drugs such as methotrexate, 6-mercaptopurine, prednisone, vincristine, cyclophosphamide, and methyl-GAG and of techniques for replacement of blood platelets and white cells cope with hemorrhage and infection. To pursue the quest for treatment that will provide long-term control of acute leukemia and to make the benefits of existing therapy available to an increased number of patients, the National Cancer Institute has organized the acute leukemia task force. The group includes members of the staff of the Institute's Medicine Branch, the Cancer Chemotherapy National Service Center, and the Clinical Branch, representatives of several nongovernmental institutions, and the chairmen of the two acute leukemia cooperative clinical groups operating under the aegis of the chemotherapy program.

Organized as a working group, the task force will, over a period of 3 to 5 years, investigate specific problems relating to treatment of acute leukemia patients. Two studies are already underway, one concerned with chemotherapy, the other with supportive therapy.

The objective of the chemotherapy study is to develop animal test systems that can be counted on to predict drug effects in acute leukemia patients with some degree of accuracy. It is likely that a battery of systems will be needed to provide a profile of drug effects. For example, one set of tumors may prove effective in selecting drugs useful in inducing remissions and another in predicting which drugs will produce remissions of the longest duration. To settle these problems, the task force is gathering data from tests in a variety of animal tumors of drugs known to be clinically useful and some that are ineffective, with a view toward identifying any correlations that may exist between screening and clinical results.

The problems in supportive therapy are of a different nature. For most hospitals and clinics, routine use of the new techniques for replacement of blood platelets and white cells is out of the question at present. Transfusions of whole blood and blood plasma no longer pose any serious problems, since methods for collecting and particularly for storing and preserving such materials are available. It is not yet possible, however, to preserve platelets for any appreciable length of time. They must be utilized within a few hours after being removed from a donor. Nor is it possible, with existing techniques, to obtain adequate numbers of white cells from normal donors, which makes it necessary to use chronic granulocytic leukemia patients as donors, since they have a white-cell surplus.

For the time being, the task force is focusing its efforts in supportive therapy on the platelet replacement problem. On one hand, members of the group were already engaged in studies of platelet preservation have intensified their efforts, and on the other, a clinical study, patterned after the cooperative clinical trials of drugs, has been initiated to define more clearly the conditions under which platelet transfusions should be used and the results to be expected.

THE OUTLOOK

Within a generation, the use of drugs in the treatment of cancer has outgrown the misunderstandings that formerly surrounded it and become a reservoir of hope for the eventual development of chemical cures. Despite the many problems still to be solved, the outlook is basically promising.

For one thing, knowledge of the biological mechanisms involved in normal and abnormal growth is accumulating at a steadily increasing rate. The progress being made, for example, in deciphering the hereditary code contained in the nucleic acids of living cells, will almost certainly have a practical bearing on the quest for chemical means of controlling malignant growth.

A second notable trend of recent years has been the increasingly widespread application of statistical techniques in designing protocols for screening and clinical trials and in interpreting the results. In addition, the Government-sponsored chemotherapy research program is now utilizing one of the most advanced and efficient automatic data processing systems in operation for storage, retrieval, and evaluation of biological information.

Finally, the newer studies being carried on within the program will make it possible in the near future to mount a more diversified chemotherapeutic attack

on all forms of cancer, while the disease-oriented approach being pursued by the acute leukemia task force facilitates research on discrete segments of the overall problem.

DEVELOPMENT OF CENTRIFUGE WITH AEC

Mr. FOGARTY. Go ahead; what progress are you making with your collaborative studies?

Dr. ENDICOTT. Several of the areas I have covered already. There is one interesting report that I would like to make which we got just today in a telephone call from Oak Ridge. We have been sponsoring the development of a special centrifuge in collaboration with the AEC. One of the investigators from the Allergy and Infectious Disease Institute has just gone to Oak Ridge and completed a study with the continuous separation of virus particles in this centrifuge. He has accomplished a remarkable purification and concentration of the virus out of the large volume of fluid in a relatively short period of time and with a very sharp peak. It looks as though it may present an opportunity for a one-step virus purification, and even at this present stage the development of the machine looks as though we can use a continuous process on a quantity, a starting quantity of at least 15 liters. With the kind of production which we are now getting from Pfizer, for one of the animal cancer viruses, in tissue culture, continuous tissue culture, I think we may well have made a very impressive move forward here in the production of purified virus for vaccines and so on.

DIRECTOR OF CARCINOGENIC STUDIES

Now, I have not said much about the carcinogenesis area. Dr. Shannon said we are very fortunate in bringing Dr. Paul Kotin from California.

Mr. FOGARTY. Is he here?

Dr. ENDICOTT. He is not here today.

Mr. FOGARTY. Give us a little of his background.

Dr. ENDICOTT. Dr. Kotin was educated in Chicago at the University of Illinois. He had his pathology training at the University of Chicago, was on the faculty at Colorado for a short time, and was in the Army during the war. He had some experience with Dr. Hueper who is one of our prominent scientists and in recent years he has been professor of experimental pathology at the University of Southern California. He is one of the world experts in cancer of the lung, particularly in the role of atmospheric pollution and chemical factors in the production of cancer of the lung and cancer in other areas.

He came to us last summer and has had now about 9 months on the job. I am tremendously impressed with his ability to attract and recruit really topflight people and to build programs very soundly in a short period of time. And in this 9-month period we have gone through negotiations with the AEC and have a program in being.

He has improvised laboratory facilities in rented space in downtown Bethesda. He has stimulated collaboration with a number of individuals at the National Institutes of Health and in various other institutions, and I think he is going to be an extremely important leader in the whole field of cancer research over the coming years.

I anticipate coming before this committee and asking for increases of major proportions for the ventures which are beginning to develop under Dr. Kotin. This whole field of chemical factors in the causation of cancer is one which must have greater emphasis in the years ahead, and we are in the planning and building stage now, but this is one area of collaborative research which I expect to give very heavy emphasis.

Mr. FOGARTY. That is good news.

Dr. ENDICOTT. To prevent cancer is a much more attractive possibility to me than curing cancer.

REMOVAL OF STIMULATING GLANDS TO RETARD RECURRENCE OF CANCER

Mr. FOGARTY. Doctor, a few years ago Dr. Huggins from Chicago appeared before this committee and told about the operations that he performed in an attempt to cure cancer. I remember he gave one example of removing the adrenal glands from a man suffering from advanced cancer and this man was out in India somewhere, hunting big game at the time Dr. Huggins was testifying. But it was not until the discovery of cortisone, that this operation was possible. He had to take a dose every day to stay alive.

What progress has been made since those days in this kind of operation and the aftereffects? Is it true they still must take cortisone to stay alive?

Dr. ENDICOTT. Yes, sir.

Mr. FOGARTY. What progress has been made in this kind of surgery?

Dr. ENDICOTT. I think by now we have a pretty definitive evaluation of the role of this kind of manipulation in the management of cancer. It has a very limited applicability, but it has become more or less standard in the armamentarium of the surgeon in dealing with cancer, particularly cancer of the breast. The objective is to deprive the cancer of certain of the natural hormones that appear to be necessary for the growth of certain kinds of breast cancer.

REMOVAL OF OVARIES

For the woman who is not yet at the menopause, the first one of these surgical endocrine manipulations is generally castration, removal of the ovaries and eliminating the hormone stimulation that comes from them. This is oftentimes coupled with the administration of male hormones.

Mr. FOGARTY. What about the side effects of male hormones? Are they pretty well controlled now?

Dr. ENDICOTT. No, sir; we have some improvement to report. Some of the drugs which have emerged from our present testing program have less masculinizing effects. This is one of the undesirable side effects—beard, enlargement of the clitoris, and change of voice. This has been decreased to some extent with some of the substituted synthetic steroids. The side effects are less severe but only 23 percent of the women respond to male hormone. Now, for those who do not respond or who stop—whose cancer returns after such therapy—

Mr. FOGARTY. You mean after the adrenal glands—

REMOVAL OF ADRENAL GLANDS

Dr. ENDICOTT. I meant first the ovary. The next point of attack is the adrenal gland. You get among women who do not respond to castration in the first place or who escape after responding for a time; you get about the same percentage who will respond to removal of both adrenals. Removal of the adrenals is a much more serious operation since the adrenals are a vital organ and one must provide a substitute for them and this is where the daily medication with cortisone comes in.

Mr. FOGARTY. Still daily?

Dr. ENDICOTT. Still daily. Presumably there is no way to escape this requirement unless one were to implant an adrenal gland and produce the hormone in the body and you are right back where you started from.

REMOVAL OF PITUITARY GLAND

Now, the surgical manipulation, the last resort, is to remove the pituitary gland and as you know, the pituitary gland is sort of the prime mover of the whole endocrine apparatus. It stimulates all of the other glands to produce their hormones and it is possible to get a fairly significant number of remissions in cancer of the breast by removing the pituitary gland. But here, again, you run into—

Mr. FOGARTY. Is that a more serious operation than removal of the adrenals?

Dr. ENDICOTT. Yes; because the pituitary gland is at the base of the brain and the surgery itself is quite complicated. The maintenance of the patient after surgery is also difficult. It requires continuous attention of a fairly good endocrinologist to keep out of trouble. The patient's ability to cope with stress and strain is seriously impaired and infection or something of that sort can carry them away quite suddenly unless the doctor is right on the job all the time. These operations have a very limited role in the management of cancer patients.

In cancer of the breast, if you look back over the last 30 years, it is very depressing, really—we have made strides in earlier diagnosis. The impact of the program, self-examination of the breast and so on is bringing patients into surgery with smaller tumors, with fewer metastases, but mortality has not changed very much. We may have to get an order of magnitude of improvement in early diagnosis to make much of a change. We are hopeful that this approach may accomplish this. The new X-ray technique will detect tumors which are so small that they can't be felt.

COMBINATION OF SURGERY AND DRUGS IN TREATMENT OF BREAST CANCER

Dr. SHANNON. May I interrupt you a moment there? I have a very strong feeling about the use of figures as Dr. Endicott used them. He said if you take cancers of the breast, it is the same mortality rate as 10 years ago, but if you see patients with cancer of the breast as we see them in the Center, who by virtue of the intelligent use of endocrines are given almost symptom-free life up to 2 years, during which time they can take care of their families, that changes the whole prospect of the individual with cancer of the breast to have an essentially sym-

tom-free period. This will not appear in the mortality figures—people who eventually die of cancer.

Take a bedridden patient with many metastases of the bone, with large open wounds, and see these closed down and to all intents and purposes, you have an almost normal person for maybe a year or two. This, I think, has in some way or another to be ground into the statistics. It will not appear otherwise, and I think that until such a time as we have cures or preventives, this is in the same category as prostatectomy and orchidectomy and adrenalectomy in cancer of the prostate, but has the advantage in that it does not provide the individual patient with a health hazard that needs care during this period. Eventually the cancer escapes and the person dies. But that year or two is important.

Dr. ENDICOTT. I was going to say, it is too early to make predictions, but I am still somewhat optimistic that the combination of drugs at the time of surgery may actually make a dent in this mortality figure. These studies are 4 or 5 years old—and with cancer of the breast, you really cannot start making any very strong statements without at least a 5-year experience because the cancers tend to recur even as late as 20 years.

But there has been a fairly impressive reduction in the rate of recurrence after surgery in a group of patients that have been given drugs at the time of surgery, when the doctor thought he was getting all of the tumor. In the ordinary course of events, the doctor thinks he is getting all of the tumor but a very substantial number of the patients have a fairly prompt recurrence, so obviously he is not. The recurrence rate has been reduced rather impressively by giving a drug at that time instead of waiting until the tumor comes back. We are getting a series of drugs now that are active in cancer of the breast. Probably some of them are better than the ones we used in this experiment. I have not given up by any means, but it is a disappointing experience to look back at the hard core statistics which are mortality statistics and realize that you have not budged them very much.

IMPORTANCE OF MEDICAL EXAMINATIONS

Mr. FOGARTY. What about the person who has had a tumor or lump in the breast removed and it is determined not to be malignant? Should they continue to get periodic examinations anyway?

Dr. ENDICOTT. Yes, sir. Every woman should have periodic examination of her breasts. Those who have had some kind of pathology probably are at somewhat greater risk. It would depend upon the nature of the lesion. In general, the statistics would suggest that the presence of pathology in the breast should make you extra careful and you should be meticulous about getting fairly frequent examination.

Now, if the lesion is malignant and is totally removed this is one of the very interesting things which has come out of the long study at Sloan Kettering Institute where they have had a cancer detection clinic over a number of years—the patient who has had cancer of the breast has a very substantially higher risk of cancer of the breast throughout the rest of her life. It may not occur on the same side. It may not be a recurrence. It may not be a metastasis. It may be

a new tumor and not infrequently is. This is true for other cancers as well. So that the cured cancer patient represents one class of patient where the annual checkup is particularly important and if you are really on your toes, you will stand a chance here to accomplish more with a cancer detection clinic than with any other patients.

GHANA FIELD STATION

Mr. FOGARTY. Tell us about your field station in Ghana.

Dr. ENDICOTT. We sent our first staff out there the first of June. The Director and administrative officer went there first in February. They have been gradually building up the staff ever since. There are approximately 22 Americans and some additional Ghanaians on the job at the present time. This has been a very difficult program.

Mr. FOGARTY. Why did you locate there and what do you expect to do?

Dr. ENDICOTT. There were several reasons for locating there. The National Institutes of Health had believed for some time that it was important to have an installation in Africa south of the Sahara to study problems, to take advantage of research activities that are peculiar to that climate and so on.

We had explored the possibility of establishing such an organization in a number of different locations and in different countries. One of the major factors in leading us to select Ghana was that Ghana itself made the decision to give a high emphasis to health programs and health research programs and established its own national institute of health and approached us with an offer to provide housing and facilities for collaborative programs. This, to a considerable extent, was in response to their invitation. We have not had this kind of offer from other places. Now, this is in a distant part of the world, and the logistics of operation are very difficult. For example, experimental animals. It is difficult to produce them on the spot. The standard American variety of experimental animal does not grow well in the tropics. Transportation by sea is so slow that this is out of the question, so that one must pretty much stick to transportation by air. There is no nonstop direct flight from the United States to Ghana and if you put materials on a plane, there are always several stops before they get to Ghana and all sorts of trouble develops en route.

Communications are very slow. Ofttimes one cannot get through on the telephone and the mails are frequently delayed and it is difficult to mount a program out there because of the problems of logistic support. I think Dr. Edgecomb, who is in charge of that laboratory, has done a very fine job under exceedingly difficult circumstances, to get going as well as he has in a period of about 9 months.

Mr. FOGARTY. Do you have a plan to have any others abroad?

Dr. ENDICOTT. No, sir. The Cancer Institute is operating this one laboratory for the NIH. The research there will perhaps mostly be infection, parasitic and nutritional diseases and not so much in the cancer field. So unless Dr. Shannon has one up his sleeve that he has not told me about, I am not going to be asked to run any more.

Mr. FOGARTY. Do you want to get rid of the one you have?

Dr. SHANNON. I don't think so. We call this laboratory the West African Research Unit because it is quite obvious that this will serve more effectively as a base for research in the surrounding countries rather than just the program in Ghana.

There are extraordinary opportunities in these areas in the study of transmission of disease and nutritional problems as well as more serious studies of a long-range epidemiological type. Certain areas, however, will be more advantageous for certain of these studies than others.

DIAGNOSTIC RESEARCH

Mr. FOGARTY. What progress are you making in diagnostic research?

Dr. ENDICOTT. This is a slow uphill business.

Mr. FOGARTY. This committee has on several occasions urged you to do more than you have been doing, even prior to your assumption of the position that you have in this area.

I notice this year you are not going ahead. You are not even leveling off but cutting it back. You are cutting back \$150 thousand in 1964.

Dr. ENDICOTT. I would like to explain that if I may. During the late 1950's, after the Pap test had been pretty well established as an effective screening test for detection of cancer of the cervix and uterus in women, it was felt that this general technique might offer major opportunities for detecting other kinds of cancer through examination of the sputum, of stomach washings, urine and so on.

FIELD STATIONS BEING PHASED OUT

A number of studies were launched to explore this and we did, in fact, establish a whole series of field stations and I think at one time there may have been as many as 20 of them.

These were set up in university frameworks and we assigned junior personnel to a number of these projects and pushed ahead with this vigorously on a number of fronts. The answers now are pretty well in. The techniques of cytology do not offer what we had hoped they would, as screening tests for these other kinds of cancer and we are now proceeding to close out these studies and close out the field stations.

They were rather expensive operations. The closing out of these field stations and these operations has furnished a substantial amount of money for reprograming in new areas.

Now, the last of the field stations will be closed this summer. So although the budget there appears to present some decrease, we are actually increasing the diagnostic program and have a number of new projects planned and ready to go.

MAMMOGRAPHY

Now, we have had some encouragement in the past year in two areas. I would like to mention them. First of all, largely as a result of some studies by a radiologist in Texas, it became reasonably clear that by using special techniques, X-ray techniques with breasts, one can

detect cancer of the breast at quite an early stage, oftentimes before it is palpable, before the surgeon himself can feel it.

We have contracts with HIP in New York City to set up a 10-year study. We are in the planning stages now. We will follow quite a large number of women over a substantial period of time.

Mr. FOGARTY. What is HIP?

Dr. ENDICOTT. Health Insurance Plan in New York State. So we think this one may really have some promise.

ENZYME TEST FOR URINARY TRACT CANCER

The other progress has come in the field of cancer of the urinary tract. This is as a result of a piece of research done at the Peter Bent Brigham Hospital in Boston, Dr. Valle's department.

They have developed an enzyme assay for LDH which is one of the enzymes which is increased in certain forms of cancer. This is handled on a small scale—

Mr. FOGARTY. Is he a recipient of a grant from the Cancer Institute?

Dr. ENDICOTT. No, sir. From the Heart Institute.

This looks as though it has real power as a diagnostic test and particularly if it is coupled with cytology to go along with it.

So we are now planning a fairly substantial field trial of this test as a new cancer screening test.

REDUCTION IN GENERAL RESEARCH SUPPORT GRANTS

Mr. FOGARTY. Why are you asking for a reduction of \$251,000 for general research support grants?

Dr. ENDICOTT. I will have to turn to Dr. Shannon.

Dr. SHANNON. These are prorated by Institute in accordance with the shift in the distribution of research grant funds. The total general research grant budget is related to the grant budget of each Institute operating under a specific limitation on the total sum of money. The total sum of money is held constant. The rate of increase in the research grant funds in other institutes is larger than that of the Cancer Institute. So the cancer contribution is somewhat smaller this year than last year with the same amount of money. The amount of money that is requested for this is \$20 million which is the 1963 figure.

EXCESSIVE SMOKING AND CANCER INCIDENCE

Mr. FOGARTY. Doctor, there has been a lot of things said about smoking and its connection with the incidence of cancer.

What do you think?

Dr. ENDICOTT. There is no doubt left in my mind that there is a very strong association between excessive smoking and high incidence of cancer of the lung. I just can't believe this is any longer in debate.

Mr. FOGARTY. They are still selling more cigarettes than ever every year.

Dr. ENDICOTT. This raises an interesting problem.

I think it would be very wise to watch the experience in Great Britain. As you probably recall, the British, as a result of a report from the Royal Society condemned the use of tobacco as an important cause of cancer.

The British Parliament took pretty aggressive legislative action and enacted a series of laws designed to reduce the consumption of tobacco.

The immediate results were to substantially decrease the consumption of cigarettes and also some changes in the tobacco market.

But it is beginning to look as though that was rather temporary and people are getting back to their old ways.

I think one of the really fascinating problems, a social problem more than a medical one, is what do you do about a situation of this kind? We are attempting to develop some research answers to this along two lines.

We are interested in exploring whether one cannot modify the cigarette in such a way as to remove the most serious cancer-causing factors as they are identified from the smoke and I think there is real room for gains here.

The other thing is that although rather a startling number of men develop cancer of the lung, there is an even larger number of men who smoke and do not get cancer.

We are captivated by the possibility of identifying a host factor here that determines which man gets cancer and which one does not, to see whether we cannot do something about this.

Now, if you will permit me, I would like to extrapolate from the laboratory—to infer what will happen in man on the basis of what happens in the laboratory.

It is perfectly possible in the laboratory to create a situation in which one chemical can have a very powerful effect in producing cancer and by the addition of another chemical to the mixture you can prevent the cancer.

If people are going to persist in smoking, and sometimes I think they probably are, then perhaps we can find a pill they can take with it.

GRANT TO DR. BJORKLUND

Mr. FOGARTY. I have just one more question, Doctor.

You remember this doctor in Sweden you were supporting for a while.

Dr. ENDICOTT. Dr. Bjorklund.

Mr. FOGARTY. What is the current status of that?

Dr. ENDICOTT. We are no longer supporting him, sir.

Mr. FOGARTY. I see.

Dr. ENDICOTT. We took the position that unless he found institutional sponsorship which was satisfactory to us by the end of the existing grant period, that we would not provide any further support.

We notified him of this in the spring. We have worked pretty hard to help him find suitable institutional sponsorship.

Several members of my staff have been to Sweden. I have corresponded with the Swedish Minister of the Interior. We have had many conferences about this with a variety of institutions in Sweden.

Finally, the State Bacteriological Laboratory in Sweden did agree to sponsor him as an applicant but then he decided that that was not acceptable to him and so time ran out, ran out in August, and we are no longer providing support to Dr. Bjorklund.

Mr. FOGARTY. Is he making any progress? Has he made any since that time?

Dr. ENDICOTT. He is. He has support still in Sweden.

Mr. FOGARTY. They think it is worth supporting and you do not?

Dr. ENDICOTT. Well, I think it is worth supporting but only under certain circumstances, sir.

SWEDEN'S HEALTH PROGRAMS

Mr. FOGARTY. The life expectancy in Sweden is pretty high, is it not?

Dr. ENDICOTT. Dr. Terry is the expert in things like this. But I think their lifespan is about the same as ours.

Mr. FOGARTY. Their infant mortality rate is better than ours.

Mr. KELLY. They are the second best.

Mr. FOGARTY. It seems to me they are doing better in the overall public health field than we are.

Dr. ENDICOTT. They have a very aggressive national program for health services in all of the Scandinavian countries.

Dr. SHANNON. In discussing this, it is only fair to point out that they are a fairly homogenous population group not characterized by any large segment of the population that are definitely below in education and health standards as compared to the bulk. I think it is difficult to compare statistics in a place like Sweden with those in the United States because here we are dealing with quite variable groups and a figure assigned to the Nation as a whole is not representative of what pertains to any specific group.

I think this is one of the reasons why we compare unfavorably to some of the so-called medically advanced countries.

Our large cities and certain of our urban areas have slum areas that are not common in Sweden. This represents a social rather than a medical problem.

I think that this must be emphasized every time when we compare statistics from one country to the United States.

Mr. FOGARTY. Mr. Denton.

POLICY ON PATENTS

Mr. DENTON. Who was going to tell me the patent policy of this Department? I asked about this earlier and was told that the Cancer Institute had had considerable experience.

Dr. ENDICOTT. Well, the basic policy of the Department, one which we apply to our own employees, and to our grantees is this:

The employee or grantee agrees to report any invention which he makes to the Surgeon General.

Mr. DENTON. Of course, that is common law anyway.

Dr. ENDICOTT. He is required to report it anyway to the Surgeon General of the Public Health Service, Dr. Terry, who has the right to determine the disposition of the rights of this invention. There are a series of alternatives which can be taken by Dr. Terry. A first device may be simply not to do anything about it but to publish the results of it in the scientific literature. If it is determined, for one reason or another, that a patent should be obtained, the determination may be that the Public Health Service, on behalf of the man, apply for a patent and retain the right to issue licenses. Ordinarily—

OWNERSHIP OF PATENT WHEN EMPLOYEE MAKES DISCOVERY

Mr. DENTON. Wait just a minute. Let us take an employee—if your employee discovers something while working for you, he reports it to the Surgeon General?

Dr. ENDICOTT. Yes, sir.

Mr. DENTON. Then it is up to the Surgeon General to determine whether or not it will be patented. Does the Public Health Service take the patent and the employee gets a shop right or license? Or how do you do that?

Dr. ENDICOTT. Ordinarily, if it is an employee, the Public Health Service applies for the patent on behalf of the employee.

Mr. DENTON. You mean the employee owns the patent when the Government hired him to get it?

Dr. ENDICOTT. He is named the inventor, but the Government has the right to the patent as far as licensing is concerned.

Mr. DENTON. I do not know why it runs this way in the Government. It would not any place else. If you do that, as far as foreign rights are concerned, he owns the patent. The Government has no rights.

Dr. ENDICOTT. The employee ordinarily assigns at the determination of the Surgeon General—assigns his rights to the Government. The Government retains the rights to issue licenses.

Mr. DENTON. You mean he assigns the patent to the Government?

Dr. ENDICOTT. Yes, sir.

Mr. DENTON. Then the Government does own the patent?

Dr. ENDICOTT. Yes, sir.

OWNERSHIP OF PATENT WHEN GRANTEE MAKES DISCOVERY

Mr. DENTON. Now, let us go to a grantee. You grant somebody funds to do research for you. He discovers an invention. What is the patent policy on that?

Dr. ENDICOTT. Essentially the same. The grantee, in accepting a grant, agrees, as a condition to accepting the grant, that he will report any inventions which he makes, to the Surgeon General who then has the right—

Mr. DENTON. Who has that patent? The grantee or the Government?

Dr. ENDICOTT. We do, ordinarily.

Mr. DENTON. You do? Have you got one of your patent clauses that you can put in the record?

Dr. ENDICOTT. Yes, sir, we can do that.

Mr. DENTON. Will you do that?

Dr. ENDICOTT. Yes, sir.

(The material follows:)

The Public Health Service patent policy relative to grants is predicated on title 45, Code of Federal Regulations, parts 6 and 8. The following is an excerpt from part 5 of the Public Health Service Grants Manual. (The patent clause relative to contracts has been inserted in this record in answer to a question under "Salaries and expenses, Office of the Surgeon General.")

505. PATENT POLICY

A. Public Health Service patent policy

Department of Health, Education, and Welfare regulations (title 45 CFR, pts. 6 and 8) provide as a condition that all inventions arising out of the activities assisted by Public Health Service grants and awards shall be promptly and fully reported to the Surgeon General. In respect to inventions reported, the institution and the principal investigator agree either (a) to refer the inventions to the Surgeon General for determination, in accordance with Department patent regulations, of the ownership and manner of disposition of all rights therein and whether patent protection on such inventions shall be sought, and, if so, the manner of obtaining, administering, and disposing of the patents in the public interest; or (b) where the institution has a separate formal patent agreement with the Surgeon General covering inventions deriving from Public Health Service support, to make a determination of ownership and disposition in accordance with its policies as approved or as modified by such agreement. In no event, shall patent applications be filed on inventions reported under (a) above, without prior written consent of the Surgeon General.

Attention is called to the fact that Public Health Service patent policy is a part of the terms and conditions of an award, and is accepted by the investigator and the institution when an application for a research grant is completed and signed. If a grant is awarded as the result of this application, the grantee institution and the investigator have joint responsibility for abiding by Public Health Service patent policy and for reporting any conflicting commitment or obligation entered into by the institution, principal investigator, or other professional personnel engaged in the project. Early reporting of inventions resulting from research grant support is required; that is, no later than at the time a manuscript is prepared for publication.

B. Amended patent agreement

In the following instances, Department of Health, Education, and Welfare procedure requires the completion of an amended patent agreement, which, when signed, becomes a part of the terms and conditions of a grant or award:

1. Where the institution proposes to subcontract with a commercial organization for a portion of the research to be conducted under the grant.
2. Where the investigator proposes to submit compounds to be synthesized and/or developed with Public Health Service support to a commercial company for screening purposes.

C. Formal reports of invention

In respect to inventions reported direct to the Surgeon General for determination under Department regulations, a formal report of invention is required in the nature of answers to 18 questions listed in the "Outline for Invention Reports" (exhibit 2). The form and other specific instructions for submission of the report will be provided upon request.

Progress reports, which may include descriptions of inventions, may not substitute for formal reports of inventions.

In respect to inventions administered under the terms of an institutional patent agreement, an annual report from the grantee institution is required, listing any inventions which have resulted during the year and the disposition of each invention made by the grantee institution. If no inventions have resulted during the year, the annual report should so state. In addition to the annual report, prompt reporting of inventions which the grantee institution has determined are possibly patentable and on which patent applications have been filed, is required.

D. Annual invention statement

In addition to the formal reports described in (C) above, an annual invention statement must be provided as part of the request for renewal of each type of Public Health Service grant and award. This statement must be submitted even if no invention has occurred during the current period of grant support for which renewal is being requested, and even if an invention to be reported was only partially supported by Public Health Service funds. The statement should include all inventions which might possibly be construed in any manner to be Public Health Service grant or award supported or related. Renewal of a grant or award will not be paid until such time as the invention statement has been received.

When a grant or award terminates and no renewal application is planned, an annual invention statement must be submitted as part of the required final progress report.

When an investigator moves to a new institution, a final invention statement must be submitted covering research conducted at the original grantee institution.

E. General research support grants (institutional grants)

Any invention first conceived or actually reduced to practice in the course of work conducted under any specific research project which the grantee institution aided through a general research support grant is subject to the provisions of the patent policy described in the foregoing paragraphs. The institution official responsible for the general research support grant will be expected to obtain annual invention statements from the principal investigators of each of these specific research projects and to incorporate them into one overall report on the general research support grant.

F. Inventions resulting from grants made in support of Federal employees

Inventions made by Federal employees are subject to the terms of Executive Order 10096, as amended by Executive Order 10930, governing inventions made by all Federal employees.

Inventions resulting from research grants made in support of full-time Federal employees in hospitals of the Public Health Service must be reported to the Surgeon General for determination under Executive Order 10096.

Inventions resulting from research grants made in support of employees of other Government agencies must be reported simultaneously to the Surgeon General under the terms of the grant agreement and to the employing agency under the terms of Executive Order 10096.

Dr. TERRY. If I may, although the problem is larger in Dr. Endicott's area than in most of our areas in the Public Health Service, we have a central patent office in the Office of the Surgeon General and as I mentioned to you the other day, when this question was raised, for a thorough discussion I would appreciate it if you would wait until Dr. David Price, who is the Deputy Surgeon General, is testifying for my Office, and he can tell you about the departmental patent board and all of the details of how we handle it.

Mr. DENTON. What I am interested in is this: I do not know of any other place but Government, when you hire a man to get an invention for you, and if he procures the invention while working for you, he gets the patent and the Government a license. All through the Government it seems that when the man gets the patent, he keeps the patent and the Government gets only the license.

Dr. TERRY. That is not the case.

Dr. ENDICOTT. No, sir; that is not the case. We get the patent and we have the rights.

Mr. DENTON. All right.

Dr. TERRY. He is designated in the patent application as the inventor but the rights go to the Government.

CANCER VIRUS ANTIBODIES

Mr. DENTON. All right. Now, in your research on viruses do you find cancer antibodies?

Dr. ENDICOTT. Well, sir, some of these viruses produce antibodies that we can detect and others do not. This presents something of a research problem because antibodies are one of the really exquisite analytical methods for studying. It is one of the peculiar aspects of some cancer viruses that they are weakly antigenic.

Mr. DENTON. What do you mean by that?

Dr. ENDICOTT. They are not very effective in causing the body to produce antibodies.

Mr. DENTON. Well, if there was a virus, there would be an antibody, would there not?

Dr. ENDICOTT. Not necessarily. Take one of the viruses you are familiar with. Let us say yellow fever virus. One exposure to this virus, if you survive it, probably will confer a solid lifetime immunity with demonstrable antibodies from then on.

Some of the other viruses do not do this. They produce an infection; the person recovers from the infection but you cannot demonstrate that there are any antibodies present, and, in fact, they may not be immune and may have the disease from the same virus several different times.

Mr. DENTON. I was surprised by your statement about being discouraged about cancer of the breast, and I say that for two reasons: When I first came to this committee 12 years ago, there was a doctor who testified, who was a surgeon. He was from New York. He told us how successful he had been with that type of operation.

The second thing is, either a year or two ago you told us that cancer on the part of men was increasing, but cancer on the part of women was decreasing. You or your predecessor.

PAP TEST REDUCING CANCER MORTALITY IN WOMEN

Dr. ENDICOTT. There is a good reason for that. I believe overall reduction in cancer mortality in women is largely attributable to the success of the Pap test. Now, there has been a very sharp reduction.

Mr. DENTON. You mean that is the one they had in Memphis?

Dr. ENDICOTT. That is a vaginal smear that detects cancer at an early stage—cancer of the uterus—which is one of the major causes of cancer deaths in women. This has fallen off pretty rapidly and makes an impact on the total figures.

Mr. DENTON. When I was down in Memphis they told me that they sometimes found cancer cells in women and they did not develop cancer and they found others where they found cancer cells and they did develop cancer. They said the important thing was to follow that up. How are you going to follow up that investigation?

Dr. ENDICOTT. We are still following the population in Memphis and probably will continue to do so for some years to come. What they were undoubtedly referring to is the very early form of cancer. There is some argument among some experts as to whether it is really cancer or whether it isn't. But it now seems reasonably clear that some of the mildest forms of cancer, so-called cancer in situ, may actually go away all by itself. Cancer of the cervix has a pretty high association with childbearing and there is more than a little reason to believe that this cancer may result from chronic irritation and following childbirth injuries.

CARRYOVER BALANCE FOR BUILDING PLANNING

Mr. DENTON. Mr. Fogarty spoke about the fact that you are carrying over a balance of \$307,000 and I believe you said that was because you had not authorized training grants, is that correct?

Mr. KELLY. This relates to the building. We have asked for authority to carry forward—we had authority in 1963 to carry forward planning funds in connection with the design of the cancer building. In fiscal year 1961 the Congress provided funds in this appropriation for the design of a new building and those funds remained available until June 30, 1963.

Mr. DENTON. You had \$9 million plus for building this cancer building in another place in the budget.

Dr. ENDICOTT. That was in another part of the budget.

Mr. KELLY. But the planning funds were provided for in the basic cancer institute.

Mr. DENTON. Is that \$307,000 the only unobligated balance you have?

Dr. ENDICOTT. Yes, sir. That is the remainder at the beginning of this fiscal year. That was carried forward from fiscal 1962.

Mr. KELLY. That is the only unobligated balance for which you have authority to carry it forward beyond fiscal 1962.

Mr. DENTON. That is what I was going to ask.

RESEARCH GRANT OBLIGATIONS

You had two meetings of your advisory council, I presume, this year.

Dr. ENDICOTT. Yes, sir.

Mr. DENTON. You will have one in May?

Dr. ENDICOTT. I think the next one will be next week, in March.

Mr. DENTON. How much is unobligated and how much is obligated for research grants? I am talking about 1963.

Dr. ENDICOTT. I can give you the obligations as of December 31. I have them with me. Obligations as of today, I do not have with me. I will have to supply that.

Mr. DENTON. Will you put that in the record?

Dr. ENDICOTT. Yes, sir.

(The information follows:)

Obligations incurred for research grants through February 1963, amount to \$42,744,904.

UNFUNDED APPROVED GRANTS

Mr. DENTON. How many projects do you have that have been approved by the advisory council and what is the amount of money that they would call for?

Dr. TERRY. That they have or have not been able to fund?

Mr. DENTON. That you have not been able to fund.

Dr. ENDICOTT. I don't believe that there are any.

Dr. TERRY. The likelihood is that the funds available to us in 1963, Mr. Denton, will be sufficient to permit us to fund all approvable projects.

Dr. ENDICOTT. As far as I can tell, that is true.

Mr. DENTON. Do you have any projects submitted to you for the year 1963 which have been approved by the advisory council which have not been funded?

Dr. ENDICOTT. Yes, sir; we have a few, but it was not because of lack of funds. This was because of the administration's decision not

to fund them. It was not because of lack of funds. There are a few such projects.

Mr. DENTON. Then you will have a few carried over?

Dr. ENDICOTT. Yes, sir. But I wouldn't intend to fund them under any circumstances.

DIFFICULTY IN RETAINING TOP SCIENTIFIC PERSONNEL

Mr. DENTON. I heard your statement about your difficulty in getting doctors to carry on this work and you are worried about the future. If that is the case, do you not think you need to step up your fellowship training the same way Mental Health has?

Dr. ENDICOTT. Well, the difficulties that I am having, sir, are that I am unable to attract and keep—not the youngsters who are finishing training programs. We have them in great supply. What happens to me all the time is that Dr. Shannon or the deans around the country take my men away from me, you see, and I am left in a predicament.

Mr. DENTON. That is up to Dr. Shannon, then.

Dr. ENDICOTT. The basic difficulty here is that I cannot compete with the salaries private industry and some of the schools pay.

Mr. DENTON. That is a statement that I have heard—that we are giving money to the medical colleges and then they are taking away our employees. Is there anything to that?

Dr. ENDICOTT. Yes, sir. It isn't just our money that is making it possible to take them away. The whole salary structure in the academic world is getting out of our range.

Now, this is particularly noticeable in the clinical areas. We have had constant experience with this over the past 2 years. So it is crystal clear in my mind that the kind of problem that we are up against—well, the chief of one of my clinical branches is a man perhaps 40 years of age, a fine investigator. He is a commissioned officer and is a medical director. I believe with his years of service, his salary is around \$14,000 or \$15,000. Within the past 5 or 6 months he has been offered at least half a dozen university posts at salaries of \$25,000 to \$35,000. He is a man with a family of about six or seven children and he is continuing in his present position as medical director at a considerable sacrifice, and of course the kinds of opportunities that are offered are to do the same type of research which he is doing with us.

I look at this man frankly as ultimately filling the vacancy left by Dr. Sessoms. But there is a very serious doubt in my mind whether he will stay with us. If it were happening in only one place it would be one thing. But the chief, usually the second and perhaps even the third man in each of my clinical branches has had repeated offers which are completely out of our price range.

What is even more difficult, is that in order to take some of these top jobs like the one which Dr. Sessoms filled, you have to ask the man to make one additional sacrifice, and that is to leave his participation in research and devote full time to program direction and to many scientists this is a somewhat unattractive prospect, unless you have something to offer in its place. Dr. Sessoms left July 1. I have been looking very actively for a replacement for him ever since. I haven't even a candidate at the present time.

Another of my associate directors, Dr. Michael Shimkin, has requested retirement effective July 1. That represents just exactly half of my top program directing staff. I really haven't completely faced up to the problem of Dr. Shimkin's replacement yet.

PROGRESS AND VALUE OF NATIONAL CANCER INSTITUTE

Mr. DENTON. One last question.

If you were asked to give a succinct statement as to what progress has been made by the Cancer Institute and why it was worthwhile for the Government to carry on this program, what would you say? You have given quite a statement as to the progress that has been made in the last year or so to Mr. Fogarty.

Dr. SHANNON. This is a very serious question. I think really, this would be helpful if Dr. Endicott could have a little time to submit this comment for the record.

Mr. DENTON. That is fine. I would like to have a short succinct answer; then if you would like to add more detail, you may.

(The statement follows:)

SUMMARY STATEMENT

A tremendous reservoir of knowledge about the collection of more than 100 diseases called cancer has come from the research conducted and supported by the programs of the National Cancer Institute since the Congress, with the establishment of the Institute in 1937, selected this instrument of attack. A great portion of this knowledge is not known to the general public at any particular time in terms of direct applied results, but is vital to research development and serves as the indispensable foundation for future advances. From this knowledge, however, has already come a large number of advances of direct benefit to mankind, both the patient and the well individual.

Although 46 million U.S. citizens now living will eventually have cancer if present rates continue (and every 2 minutes someone dies with cancer), there are today 1,200,000 former cancer patients alive who were treated and have been free of evidence of the disease for at least 5 years. In 1963, patients who will be saved from cancer will number 177,000, representing 1 in every 3 cancer patients. This represents real progress since the 1930's when only one patient in every five was saved.

Perhaps the best example of this progress is the dramatic decline during the past two decades in the death rate for uterine cancer of about one-half in white women and one-third in nonwhite women. Before 1940 this form of cancer was the leading cause of cancer deaths in women; it is now the third leading cause. Two research developments are largely responsible for this decline in mortality and for the ultimate prospect of virtually eradicating this type of cancer: (1) the Papanicolaou technique for detecting cancerous cells by microscopic examination after staining of the cells shed by uterine tissue; and (2) epidemiological studies which found that cancer of the uterine cervix can exist in a stage called carcinoma in situ for several years before becoming frank, invasive cancer, presenting the usual symptoms, such as bleeding. The demonstration of the value of the "Pap smear test" on a large scale for finding early uterine cancer cases and aiding in diagnosis was made by an Institute-supported study involving 108,000 women, in which about 800 new cases of cancer were found, fully 90 percent of which were unsuspected. Successful treatment could be applied early in most of these cases before the cancer became invasive with spread to other sites, and in a sample screening of the same population a year later, the invasive cancer rate had fallen from 3.4 to 0.3 per thousand.

Great research efforts have been expended in the search for other early cancer detection tests. None has been as successful as the "Pap smear test," but in several cases successes have been achieved in some types of cancer, such as those that elaborate chemical substances in the blood or urine that may be measured by sensitive laboratory techniques. A new research lead is the use of soft X-

rays in the earlier detection of cancer of the breast, a form of cancer that currently takes the lives of about 25,000 women annually in the United States (64,000 new cases will be diagnosed in 1963). Preliminary results were successful enough to warrant a large-scale pilot study which the institute is currently supporting, involving about 20,000 women; if the pilot study results are favorable, a long-term investigation will be made to obtain full evidence of the value of the technique.

Surgery and radiation have been mainly responsible for the gains made in treatment of cancer, but drug therapy is making progress and is the hope of the future in cancer treatment. Prior to 1940, essentially no chemical agents were available to benefit those cancer patients who could not be helped with surgery or radiation (mostly patients with disseminated cancer). Today, however, several chemical agents are now providing benefit, with prolongation of comfortable life, even if not curative.

For the first time, a high proportion of patients with any one type of cancer has been freed of the disease (as evidenced by a highly sensitive hormonal test) through the use of drugs alone, and several of these patients have now lived for more than 5 years with no indication of cancer. The type of cancer is choriocarcinoma, a highly malignant tumor sometimes arising in the uterus during or following pregnancy, and the drug is methotrexate. This outstanding accomplishment was made by Dr. Roy Hertz, Chief of the Institute's Endocrinology Branch, and his coworkers. Very recently, Dr. Hertz and his colleagues have increased the proportion of successful treatment to a level of about three-fourths of the patients, by combining methotrexate with Actinomycin D, an antibiotic.

Fifteen years ago, half of all children with acute leukemia died within 3 or 4 months. Largely as the result of drug treatment, significant improvements have been achieved in the management of the illness, resulting in a fourfold increase in median survival time. Some of the most useful drugs include methotrexate, 6-mercaptopurine, cyclophosphamide (Cytosan), prednisone, Vincristine, and methyl-GAG (methylglyoxal-*bis*-guanyldiazone). Additional successes have recently been achieved with transfusion techniques of white blood cells and platelets to combat infection and hemorrhage.

Myleran is currently the best available drug for chronic granulocytic leukemia and chlorambucil for chronic lymphocytic leukemia; they represent other examples of drugs developed and tested through enormous efforts made in the last 15 years. Major impetus was given to this area of work by the establishment of the Institute's national, voluntary cooperative cancer chemotherapy research program in 1955. Under this effort, thousands upon thousands of chemical agents have been systematically screened for activity against tumors. The relatively few found to damage tumors are further tested for potency and toxicity. Finally, selected agents are studied to provide maximum safety and are evaluated in cancer patients. This program has added new compounds to the physician's armamentarium of drugs useful for treating cancer patients, and with the maturing of the program a steady flow of new agents is now receiving evaluation in clinical studies involving many types of cancer.

Much has been learned about causative factors of cancer during the past two decades. In addition to gaining understanding of the role of radiation in cancer induction, much has been learned about chemical agents that can produce cancer. To date, over 450 chemicals of various types have been shown to induce cancer in animals, and some of these have been implicated in human cancer causation. Steps have been taken to protect man from these agents with prevention of the disease; e.g., prevention of cancer of the lungs and other parts of the respiratory tract in chromium industry workers and cancer of the urinary bladder in certain chemical industry workers. Considerable understanding of the various factors that play a role in chemical cancer causation have been elucidated, such as dosage response, combinations of different chemical agents, routes of exposure, hereditary factors, and so on.

More recently, the importance of viruses in cancer induction has been elucidated. Viruses have been established as a cause of leukemia in mice, and virus particles found in the blood of leukemia patients as seen with the electron microscope resemble closely those seen in blood of the leukemic mice. That man may someday be successfully vaccinated against at least some kinds of tumors is suggested by the successful immunization of some animals against some types of virus-induced tumors. Although there is not now any evidence that any human cancer is caused by a virus, two viruses isolated from man which may produce mild respiratory disease (adenoviruses types 12 and 18) have been shown to

produce tumors in hamsters. Moreover, lung cancer has been produced in mice with a combination of an influenza virus and certain gasoline hydrocarbon fractions, indicating need for extensive followup work on combinations of agents of potential cancer-causing importance. Very extensive research efforts are currently underway to evaluate the role of viruses in human cancer.

Great progress has been made since the Institute was established in the techniques of collecting vital statistics on cancer (comparative data on variations in the incidence and mortality of cancer by age, sex, race, geographic region, marital status, type, primary organ site of the disease, etc.). Extensive reports on this type of information have been published on several occasions, the latest being in Monograph No. 6 of the Journal of the National Cancer Institute, published by the Institute as one of three major scientific periodicals in the United States devoted to cancer research. These techniques have also been vital for the sound evaluation of end results with different treatments, and similar approaches have provided greatly improved foundations for screening of agents for antitumor or cancer-causing effects and for the sound design of clinical trials evaluating new drugs in man. These modern statistical techniques also have strengthened epidemiological studies in man. Such studies seek to find important new research leads or preventive measures through correlations found between disease and factors in man's environment or man's habits, such as the examples given above in chromium and chemical industrial workers.

Hundreds of other examples could be given of the progress made since the Institute was established, and indeed such examples are available in the extensive scientific literature in the numerous sound scientific periodicals that form such a vital part of the mechanism in science upon which progress in medical research depends.

Today the NCI supports the great majority of research on cancer in the United States. It does this by the work of its own scientific staff, by grants, and by contracts, results from which are so inextricably interwoven into a total fabric of scientific knowledge about cancer that it is impossible to define precisely the boundaries of NCI's contribution. What can be said with assurance is that this contribution has been vital. The administration of these cancer programs as the focal point in a national setting requires an uncommon blending of scientific and administrative skills difficult to find, particularly in an area with such broad scope and complexity as cancer research. The organization of the NCI brings together in one place those who both conduct research and administer these broad, nationwide programs, to form a unique device for carrying out such an activity. The research is continually evaluated not only by staff, but by the Nation's top scientific leaders from universities, hospitals, research institutes, and other organizations. This sizable volume of research has been judged to be of a high order of excellence, and it is increasingly involved directly and indirectly with most of the advances being made against cancer. Cancer has been one of the most formidable problems in the history of medical science; much remains to be done. Behind all these efforts, of course, is the cancer patient who is refractory to radiation and inaccessible to surgery, for whom something more must be done. The Congress showed great foresight in creating as the focal point of a national effort the National Cancer Institute for the mechanism of attack, and steady progress has been made. The degree of success in the future will continue to depend, to a great extent, on both the level and type of support made available.

CANCER RESEARCH DEVELOPMENTS SINCE 1937

Since the Congress established it in 1937, the National Cancer Institute has been struggling with one of the most formidable problems in the history of medical science. While such awesome maladies as smallpox, diphtheria, and rabies have long since yielded to therapeutic or prophylactic procedures devised through diligent investigation, cancer has not yet done so even though a large, well-supported and most determined assault has been made upon this group of diseases over the past several years. Much has been learned over the past two decades about the nature of cancer, including its diverse manifestations and its effect on life processes. Some of this knowledge has led to improve medical management of cancer, resulting in benefit to cancer patients and the saving of lives. Other knowledge forms the basis for improved medical management in the future. But the precise nature of the cancerous process, the key to the ultimate solution of this grave and stubborn problem, continues to elude science.

Statistics on cancer may seem paradoxical. In the United States:
There will be 280,000 cancer deaths in 1963.

This represents one cancer death every 2 minutes or one death in every six deaths (16 percent), exceeded only by deaths from diseases of the heart and circulatory system.

There will be 530,000 new cancer cases diagnosed in 1963.

There will be 815,000 cancer patients receiving medical care in 1963.

If present rates continue, 46 million people now living will eventually have cancer.

This is 1 person in 4, or 2 families in 3.

About one-half of cancer deaths are among those under the age of 65 years.

But—

Today, 1,200,000 former cancer patients who were treated and have been free of evidence of the disease for at least 5 years are alive (and 700,000 additional ones will be added to the group during the next 5 years).

This year, 177,000 patients will be saved from cancer with surgery and radiation treatment. This represents about 1 patient in 3. (In the 1930's only 1 in 5 was saved.)

A tremendous reservoir of knowledge about cancer has come from the Institute's 25 years of research. Only a portion of this is visible at any particular time in terms of direct applied results. The greatest part of this knowledge is not known to the general public, but is vital to research development and serves as the indispensable foundation for future advances. The NCI staff has contributed substantially to this fund of knowledge, and it has administered programs providing support for the greatest portion of such knowledge contributed elsewhere in the United States. Its own researches and those of its grantees and collaborators have in turn stimulated the work of still others, all of them so inextricably interwoven into the total fabric of scientific knowledge about cancer that it is now impossible to define the boundaries of the NCI's contribution. What can be said with assurance is that this contribution has been vital. A few of the applied and more apparent basic results of the research can be more readily cited.

Today one-third to one-half of all cancer patients may hope for recovery, as a result of hard work in both research and public education. Perhaps the best example is the dramatic decline during the past two decades in the death rate for uterine cancer of about one-half in white women and one-third in nonwhite women. Prior to 1940 uterine cancer was the leading cause of death from cancer in women; it is now the third leading cause.

Two exciting research developments are largely responsible for this decline and for the ultimate prospect of virtually eradicating uterine cancer. The late Dr. George N. Papanicolaou of Cornell University Medical School developed a technique for microscopically examining cells shed by uterine tissue. The presence of cancer cells in these specimens indicates the possibility of cancer in the tissue from which the cells came. Other epidemiological studies found that cancer of the uterine cervix can be present in a stage called *carcinoma-in-situ* for several years before becoming frank, invasive cancer presenting the usual symptoms, such as bleeding.

To test the possibility that the cell examination might be employed to find cases and aid diagnosis, the National Cancer Institute gave grant support to Dr. Douglas Sprunt and colleagues of the University of Tennessee Medical School to test large numbers of women in Tennessee. The test worked: among 108,000 women tested for the first time, about 800 cases of cancer were detected. About half of these proved to be *carcinoma-in-situ*, fully 90 percent of which were totally unsuspected. The other 400 cases were invasive cancer, 30 percent of which were also unsuspected. A year later 33,000 of these same women were retested and 83 cases of cancer were detected, of which 72 were preinvasive and 11 invasive, or later stage. The invasive cancer rate on the second screening dropped from 3.4 to 0.3 per thousand. In other words it was only one-tenth as high as on the first screening. Studies in several other communities produced similar results.

When we consider that at the preinvasive stage the disease is practically 100 percent curable, we can understand why, as soon as these facts were communicated to the medical profession and the lay public, the cell examination test became widely used and may be credited with a good share of the improvement in the uterine cancer problems.

At this stage in our understanding of the nature of cancer, our greatest hopes for saving lives ride on such early detection techniques. NCI scientists and grantees are currently working on early detection by X-ray of breast cancer, the killer of nearly 25,000 women annually; and on other techniques in identifying kidney and bladder cancers, and of other specific sites.

Some advances in treatment have been made. Surgery and radiation have been mainly responsible for the gains reported, but drug therapy is making progress and is the hope of the future in cancer treatment. Prior to 1940 essentially no chemicals were available to benefit those cancer patients who could not receive help from surgery or radiation (mostly patients with disseminated cancer). Today, however, several chemical agents are now providing benefit to the cancer patient, even if not curative.

For the first time, a high proportion of cancer patients of any one type have been freed of the disease (as evidenced by a highly sensitive hormonal test) through the use of drugs alone, and several of these patients have now lived for more than 5 years with no indication of cancer. This accomplishment was made by Dr. Roy Hertz, Chief of the Institute's Endocrinology Branch, and his coworkers. The type of cancer is choriocarcinoma, a highly malignant tumor sometimes arising in the uterus during or following pregnancy, and the drug is methotrexate. Very recently, Dr. Hertz and his colleagues have increased the proportion of successful treatments to a level of about three-fourths of the patients, by combining methotrexate with Actinomycin D, an antibiotic.

Although women with breast cancer generally require surgery, treatment of advanced cases with the male hormone, testosterone propionate, was introduced in 1939 with some benefit to the patient. Regression of the disease results in one of five cases, but the treatment must often be suspended because it causes distressing masculinizing effects. The National Cancer Institute's nationwide cooperative chemotherapy program has introduced a new substance related to the male hormone, 2-M-DHTP (2-alpha-methyl-dihydrotestosterone propionate), which has proven equally as effective without, or with less of, the undesirable side effects.

Under the auspices of the Institute's chemotherapy program, large-scale clinical trials were also undertaken of drug therapy in conjunction with surgery. In one such trial, women operated on for breast cancer were given an alkylating agent, ThioTEPA, on the day of surgery and on the 2 following days. Follow-up so far indicates that recurrence has been less frequent among women who received the drug than among those who had surgery alone.

A technique for administering highly toxic but effective agents to the disease area with considerably reduced danger to the patient, called the isolation-perfusion technique, was introduced by Dr. Oscar Creech, Jr., and his colleagues, grantees of the National Cancer Institute at Tulane University. While the tumor-bearing area is isolated from the rest of the body by diverting the blood circulation through a heart-lung machine, drugs are introduced into the blood of the isolated area in much higher doses than could be given to the patient by ordinary means. Malignant melanomas and sarcomas have responded to this form of treatment with some successes.

Fifteen years ago, half of all children with acute leukemia died within 3 or 4 months. Largely as a result of drug treatment significant improvements have been achieved in the management of the illness, resulting in a fourfold increase in median survival time. Dr. Sidney Farber, an NCI grantee at the Children's Cancer Research Foundation in Boston, has demonstrated that methotrexate suppressed the disease temporarily. Dr. Joseph B. Burchenal and other grantees at Memorial Sloan-Kettering Cancer Center in New York have shown that 6-mercaptopurine also induces remissions. Clinical trials supported by the National Cancer Institute have further proved the usefulness of an alkylating agent, cyclophosphamide, and, in the Clinical Center at Bethesda, Dr. Emil Freireich, III, has had additional success with a new plant extract, Vincristine. These drugs can induce several remissions of childhood acute leukemia, extending comfortable life for the patients and affording them the benefit of additional treatment.

In another approach to the acute leukemia problem, National Cancer Institute clinical investigators have developed a technique of blood reinforcement to reduce hemorrhage and infection which often cause death before drugs have had time to take effect. Hemorrhage in leukemia patients can result from a deficiency of blood platelets and consequently failure of the blood to clot properly. Dr. Emil J. Freireich and co-workers in the Institute's Medicine Branch devised improved methods of collecting and transfusing platelet-rich blood plasma. They

also adapted these procedures to the replacement of white blood cells which are needed in the blood to combat infection.

Important work has been done by NCI staff and grantees on chronic leukemia, which is the form often found in older patients. Nitrogen mustard, related to the compound used for a war gas in World War I, was found helpful in treating this disease in the early 1940's, and since then hundreds of other alkylating agents have been developed and tried. In England, Drs. Alexander Haddow and G. M. Timmis of the Chester Beatty Research Institute working under National Cancer Institute grants, developed myleran, considered the best drug available for chronic granulocytic leukemia. Another compound, chlorambucil, has also been demonstrated to be helpful in treating chronic lymphocytic leukemia and some types of lymphomas and other solid tumors.

Clinical research in cancer chemotherapy stands largely on a base of animal experimentation which has produced an important body of data on the action of drugs and response to medication. One of the basic problems is that after awhile, leukemia seems to develop resistance to a particular drug. Dr. Lloyd W.

Law of the National Cancer Institute demonstrated that this resistance is a genetic phenomenon, originating in the mutation of some cells. These cells become dominant as the others are destroyed by the drug, and the medication therefore becomes ineffective. This phenomenon suggested the technique of using series of drugs, sometimes in combination, to prolong effective treatment. Such combination drug treatment has been successfully demonstrated in patients, and additional combinations are currently under study.

Drug therapy has long been a hopeful and promising area for improvement in the management of certain types of cancer that are poorly responsive to other methods and offers the only hope for those cases in which the tumor tissue is widely disseminated since surgery cannot be successfully used and radiation is often not sufficiently effective. The latter category includes, of course, the leukemias and lymphomas. Although serious research has been done previously on the development of chemotherapeutic agents, this area received major impetus only after the establishment of the National Cancer Institute's national, voluntary cooperative cancer chemotherapy research program in 1955. Under this effort, hundreds of thousands of compounds of all kinds have been systematically screened for activity against animal tumors. The relatively few found to be able to damage tumors are further tested for potency and toxicity. Finally selected agents are evaluated in cancer patients. This program has added new compounds to the physician's armamentarium of drugs useful for treating cancer patients, and with the maturing of the program a steady flow of new agents is now receiving evaluation in clinical studies with advanced cancer patients who have little other hope.

What factors actually cause cancers? Scientists have devoted their lives attempting to solve this mystery. They have studied a large number of aspects, from cell structure and chemistry to such personal and environmental factors as smoking and air pollution. These latter types of studies require extensive information on the distribution of cancer among different population groups. The National Cancer Institute carried out the first large-scale survey in 10 metropolitan areas of cancer incidence in the United States in 1938 and repeated the operation in 1948 to produce comparative data, on variations in the incidence of cancer by age, sex, race, geographic region, marital status, and type and primary site of disease. The most recent broad-scale compilation of this type of information was published in 1961 as Monograph No. 6 of the Journal of the National Cancer Institute, one of three major scientific periodicals devoted to cancer research in the United States.

For the past 10 to 15 years the clues have pointed to viruses as particularly likely suspects for at least some types of cancer. In the early 1900's Dr. Peyton Rous, of the Rockefeller Institute, produced fowl tumors with cell-free extracts and demonstrated that they were virus induced. A few other virus-induced tumors were known by mid-century, but new impetus was given to cancer virology research by two findings in the 1950's: (1) Dr. Ludwik Gross, of the Veterans' Administration, succeeded in producing leukemia with a virus-containing, cell-free extract administered to newborn mice; and (2) Dr. Sarah E. Stewart, of the National Cancer Institute, attempting to study further the phenomenon reported by Dr. Gross produced no leukemia, but rather large number of salivary gland tumors in animals with cell-free extracts. Then in collaboration with Dr. Bernice E. Eddy, of the Division of Biologics Standards, National Institutes of Health, Dr. Stewart was able to grow large amounts of virus in tissue cultures of mouse

embryo tissue by inoculating the tissue cultures with cell-free tumor extracts. By this means they succeeded in increasing the biological activity of the virus (called polyoma virus) so that it not only produced more than 20 different kinds of tumors in mice, but even crossed species barriers (previously believed by many to be impossible) to cause tumors in rats and hamsters.

Dr. Stewart demonstrated the possibility that vaccination might someday prevent some cancers in man when she found that mice did not develop tumors when inoculated with a mixture of polyoma virus and serum containing antibodies to the virus, or when given separate but simultaneous inoculations of virus and antiserum. Subsequently, Dr. Charlotte Friend, a grantee at the memorial Sloan-Kettering Cancer Center, who induced a different type of cancer with a virus, also developed a killed-virus vaccine that protects mice against this type of tumor. A vaccine that reduces the frequency with which virus-caused benign tumors in rabbits become malignant was also developed by Drs. Yohei Ito and Charles A. Evans, Institute grantees at the University of Washington. These investigators also demonstrated that the nucleic acid portion of the virus (freed of its protein coat) could produce tumors, indicating that, like poliomyelitis, the disease could be produced with an incomplete virus. Earlier, investigators at the Sloan-Kettering Institute in collaboration with those of the NCI demonstrated a similar finding with polyoma virus.

The discovery of virus particles in the blood of leukemia-bearing animals by Dr. John B. Moloney in collaboration with Dr. Albert J. Dalton, both of the National Cancer Institute, provides an exceptionally useful prototype for the development of approaches to human virus-leukemia studies. The virus producing this type of leukemia was discovered by Dr. Moloney, and he and Dr. Dalton worked out a method of recovering the virus in essentially pure form by spinning the blood at high speeds in a centrifuge and following its purification by means of electron microscopy.

An important recent piece of research by Dr. J. Trentin and coworkers at Baylor University in Texas bears out a longstanding suspicion that viruses which cause acute infections in man may also play a role in causing cancer. Dr. Trentin inoculated hamsters with human adenovirus 12, which may cause mild respiratory disease in man, and tumors developed in the animals. At the National Institute of Allergy and Infectious Diseases, Dr. Robert J. Huebner and colleagues, using adenoviruses 12 and 18, have obtained similar results.

Working in the opposite direction, so to speak, Dr. Hilary Koprowski and colleagues, NCI grantees at the Wistar Institute in Philadelphia found that simian virus 40, a monkey virus shown by Dr. Eddy, of the Division of Biologics Standards, to also produce tumors in hamsters, caused bizarre changes in adult human cells growing in tissue culture, changes that were passed on to subsequent generations of cells. Dr. Alan Rabson and colleagues at the National Cancer Institute, Drs. Harvey Shein and John F. Enders at Harvard University, and Dr. M. Hilleman, of the Merck Institute, have made similar observations.

Is it possible that virus may interact with chemicals in the environment to cause cancer? Results so far suggest that this possibility deserves further intensive investigation. At the University of Southern California, Drs. Paul Kotin and Hans L. Falk, former grantees (now staff members) of the National Cancer Institute, found that mice exposed to influenza virus plus air polluted with ozonized gasoline fractions developed lung tumors similar to the most common type of lung cancer in man. Neither the virus nor the chemically polluted air alone caused such tumors; they appeared only when the two were combined.

Research on viruses as a possible cause of human cancer continues with the use of tissue culture for exploration of their role in malignant change. Under the leadership of Dr. Wilton R. Earle, tissue culture has been a major area of research in the National Cancer Institute from its establishment. Dr. Earle has pioneered many developments in tissue culture, several of which formed the foundation for many advances dependent upon tissue culture techniques, including the important successes in the poliomyelitis area, and now in cancer virology. Dr. Earle and his coworkers developed large-scale cultures of cells, which have become essential in such operations as vaccine production. This team also formulated an entirely chemically defined medium that supports cell growth without the addition of human or animal serum, thus eliminating the possibility of contamination by viruses or other extraneous material.

Environmental cancer research concerns one of the best areas for control through prevention. Drs. Joseph Leiter, Michael B. Shimkin, and Murray J. Shear, of the National Cancer Institute, were one of the first groups of scientists

to show that cancer-causing agents are present in the atmosphere. They reported in 1942 that tars extracted from the atmospheric dusts of several American cities produced sarcomas in mice. Identification of cancer hazards arising from industrial processes makes it possible to take corrective measures. For example, workers in the chromate- and chromium-compound-producing industries are now being protected as a result of investigations by Dr. W. C. Hueper, of the National Cancer Institute, and by Dr. Anna M. Baetjer, of Johns Hopkins Hospital in Baltimore. Dr. Hueper, an internationally recognized investigator in his field, recently shared with a Russian scientist a \$10,000 award given by the United Nations General Assembly for outstanding scientific research on environmental causes of cancer.

Not only do environmental conditions often beyond the individual's control contribute factors to the causation of cancer, but personal habits as well may do so. Cigarette smoking, for instance, has been found to be linked to the sharply increased incidence of lung cancer over the last 30 years. Statistical studies in this country and abroad have shown that cigarette smoking considerably increases an individual's risk to lung cancer. Research thus far has not disclosed, however, the precise mechanism accounting for this increased risk, and much investigation continues.

National Cancer Institute scientists have been responsible for many other important fundamental scientific observations related to the cancer problem in one way or another. The biophysicist, the late Dr. Egon Lorenz, discovered that mice exposed to a lethal dose of X-radiation could be protected by injection of bone marrow from mice of the same strain. He and his colleagues also found that marrow from other strains and even from other species was protective, though to a lesser extent. Dr. Howard B. Andervont, former Chief of the Laboratory of Biology and now scientific editor of the *Journal of the National Cancer Institute*, has made many basic contributions to biomedical research relating to viruses, polycyclic hydrocarbons, hormones, and heredity. He contributed importantly in studies demonstrating conversion of strains of mice in which breast cancers occurred infrequently to those with a high incidence of such tumors by foster-nursing the animals with milk containing the mouse mammary virus. He was also the first to demonstrate transmission of this virus in the seminal fluid of mice. In studies of chemical carcinogenesis, Dr. Andervont showed that the nature and duration of the cancer-inducing stimulus influenced the biological properties of the cancer. Numerous other examples could be given.

Twenty-five years ago the Congress saw the need for a full scale research attack on cancer. Members foresaw that, with the control of most bacterial diseases by chemical agents, chronic and degenerative conditions such as cancer and arthritis would become major public health problems in the future. Time has proved them right in the identification of research needs; the work of the National Cancer Institute staff, its grantees, and associates during the past quarter century has justified their selection of this instrument of attack.

Today the NCI supports the great majority of research on cancer in the United States. It does this by the work of its own scientific staff, by grants (2,100 of them in fiscal year 1963) totaling \$61 million; and by contracts currently totaling about \$35 million in value. The administration of these cancer programs as the focal point in a national setting requires an uncommon blending of scientific and administrative skills difficult to find, particularly in an area with such broad scope and complexity as cancer research. The organization of the NCI brings together in one place those who both conduct research and administer these broad, nationwide programs, to form a unique device for carrying out such an activity. The research is continually evaluated not only by staff, but by the Nation's top scientific leaders from universities, hospitals, research institutes, and other organizations. This sizable volume of research has been judged to be of high order of excellence, and it is increasingly involved directly and indirectly with most of the advances being made against cancer. An organization that soundly blends the doing of research and the administration of support programs was not created easily, nor is it easily maintained. To remain among the world's great medical research organizations, it requires adequate support, a well-trained staff able to lead as well as to do, and the proper blending of concepts, ideas and efforts from both government and nongovernment activities. Behind all these efforts, of course, is the cancer patient refractory to radiation and inaccessible to surgery, for whom something more must be done. The degree of success of these efforts depends, to a great extent, on both the level and type of support made available.

Dr. TERRY. One other thing that I would like to say. The problems that Dr. Endicott has described about the Cancer Institute are not confined to that Institute. These are problems that we are facing particularly at NIH, but also throughout the entire Public Health Service. Being in a position where we are noncompetitive with the institutions for which we must compete for our real leadership in the Public Health Service, we do not expect to be able to compete with industry, or the private practice of medicine. But at the same time we are not even able to compete with medical schools.

Mr. DENTON. Thank you. We will adjourn until 10 o'clock.

MORTALITY, MORBIDITY, AND COST OF CANCER

Statistics of the annual number of deaths and total current number of disabilities caused by the major diseases dealt with in the National Cancer Institute, and the estimated annual cost to the Nation :

I. Cancer deaths in 1961 (unpublished data supplied by the National Office of Vital Statistics Division) :

Buccal cavity and pharynx-----	6,322
Digestive system-----	92,754
Respiratory-----	43,115
Breast-----	24,542
Genital organs-----	39,256
Urinary organs-----	13,040
Other sites-----	28,046
Leukemia-----	12,873
Lymphomas-----	13,554
Total, all sites-----	273,502

II. Cancer disability in 1961 (estimated on the basis of data supplied by the National Cancer Institute and the National Health Survey Division) :

(a) Estimated cases under treatment-----	815,000
(b) Estimated person-days of disability (these estimates have a large margin of error) :	
Restricted activity-----	40,000,000
Sick in bed-----	24,600,000

III. Cancer's cost to the Nation in 1961 :

- (a) Hospital bill—\$350 million (estimated by the American Cancer Society).
- (b) Loss of income—\$210 million (based on the American Cancer Society estimate of an annual loss of 50,000 man-years due to cancer illness and an average annual income of \$4,200). This minimal estimate includes an allowance for loss of productivity due to retirement for cancer disability, but not the loss of potential productivity because of a cancer death during the working years.
- (c) The economic effect of the loss of services of executives and skilled workers through cancer illness is difficult to calculate. Estimates based on the average annual contribution per member of the labor force (age 18-65) to the gross national product would indicate that cancer brings about a loss to society in goods and services valued at approximately \$15 billion per year.

HIGHLIGHTS OF PROGRESS IN RESEARCH ON CANCER IN 1962

Items of Interest on Research Studies Conducted and Supported by the National Cancer Institute

CAUSATION

Newly isolated virus causes leukemia and red cell disease in mice

A virus that causes leukemia and a disease involving extreme proliferation of immature red blood cells and massive enlargement of the spleen in mice has been isolated in the Laboratory of Viral Oncology by Dr. Frank J. Rauscher. The

virus has a number of characteristics that should make it useful for rapid testing of potential antitumor and antiviral compounds.

As early as 7 days after inoculation of a large dose of virus into newborn or weanling-age mice, immature red cells began proliferating, and in another week the spleen was enlarged to 35–50 times normal weight in virtually all the animals. Within 25 to 35 days, 50 percent of the mice died. Those surviving for more than 40 days almost invariably developed lymphocytic leukemia, culminating in death 2 to 3 months after inoculation.

The animals' response to the virus depended on the size of the dose and on their age at the time of inoculation. The larger the dose, the sooner spleen enlargement and death occurred. The older the mice, the less likely they were to die of the early disease, and as a result the incidence of leukemia was increased. The virus had essentially the same effect in one random-bred and eight inbred strains of mice and in an inbred strain of rats.

The dual type of disease it induces, the short time it takes to cause both red-cell proliferation and leukemia, and its lack of age- and strain-specificity clearly differentiate the virus from others that cause leukemia in mice and rats. In addition, antisera to three other mouse leukemia viruses have little or no effect on its activity.

As shown by electron microscope studies of plasma and megakaryocytes from diseased mice, the mature virus particles, like those of other mouse and rat leukemia viruses, measure 90–100 millimicrons in diameter and consist of a dense core surrounded by two outer membranes.

Dr. Rauscher has also found that the blood of infected mice contains large amounts of the virus at least as early as 16 days after inoculation. A similar phenomenon occurs in mice and rats inoculated with the leukemia virus previously isolated by Dr. John B. Moloney, Laboratory of Viral Oncology. (Journal of the National Cancer Institute 29: 515–541 (1962).)

NCI scientist isolates leukemia-inducing nucleic acid from mouse tissues

Nucleic acid that induces leukemia in mice has been isolated by Drs. John B. Moloney and Albert J. Dalton, Laboratory of Viral Oncology. Extracted from tissues of mice and rats bearing the Moloney virus-induced leukemia, the nucleic acid reproduced the disease in mice and led to the formation of whole virus particles in the animals.

About one in every nine mice inoculated with nucleic acid preparations when newborn developed leukemia after intervals ranging from 18 to 24 weeks. The incidence was lower and the latent period longer than those following inoculation of intact Moloney virus.

Particles resembling those found in animals bearing the virus-induced leukemia were seen through the electron microscope in bone marrow cells of mice with the nucleic acid induced leukemia. Assays of cell-free material from these animals provided additional evidence of the formation of virus in their tissues. Within 8 weeks after the assays were begun, 12 percent of the test animals died of leukemia, and more than half showed gross evidence of the disease.

Treatment of the nucleic acid preparations with the enzyme ribonuclease destroyed their leukemia-inducing ability, but treatment with deoxyribonuclease had no effect. This result was in accord with previous indications that the Moloney virus contains ribonucleic acid (RNA).

This work, reported by Dr. Moloney at the Eighth International Cancer Congress in Moscow, adds the Moloney leukemia to a long list of viral diseases of plants and animals that can be reproduced with nucleic acid preparations.

A monkey virus causes abnormalities in cultures of adult human cells

Dr. Hilary Koprowski, of the Wistar Institute of Anatomy and Biology in Philadelphia, has reported that a monkey virus can infect adult human cells in tissue culture and cause abnormalities in cell structure and chromosomes.

The virus, known as Simian Virus 40, was first isolated in 1960 from monkey kidney tissue being used in production of a polio vaccine. Since then, it has been found to cause tumors at the site of injection in newborn hamsters and degenerative changes in tissue cultures of human embryos. The work now reported concerns the effects of SV40 on cultures of tissues from the skin and mouth of adult human donors.

The virus produced a variety of changes that affected cell structure and growth pattern as well as the number of chromosomes per cell and the structure of some chromosomes. The changes occurred 8 to 14 weeks after SV40 was inoculated into the cultures.

The altered cells seemed to have a growth advantage over the remaining normal ones. The latter eventually were overgrown, and the cultures became wholly abnormal. Once that happened, the cells began multiplying far faster than those in cultures that had not been exposed to SV40.

At the time the report of the work was prepared, the cells retained their abnormal characteristics, and virus had been recovered from all cultures in samplings taken 12 to 96 days after the experiments began. The report describes the change as a "transformation," but its significance is not yet clear. (*Journal of Cellular and Comparative Physiology* 59: 281-292 (1962).)

Vaccine increases regression rate of virus-induced tumors

The development of a vaccine that increases the rate at which virus-induced rabbit papillomas regress instead of becoming malignant has been reported by Dr. Charles A. Evans, of the University of Washington, in Seattle. The work provides evidence that vaccination can enhance natural resistance to one form of cancer in animals.

Virus-induced papillomas in domestic rabbits are benign tumors that usually become malignant but sometimes regress completely. The nature of the regression process is not understood. Though antibodies to the virus are regularly present in tumor-bearing animals, they have not been shown to have any relationship to the regression phenomenon.

Previous attempts to alter the regression rate were unsuccessful. It could not be decreased by treating rabbits with cortisone or with serum from rabbits having persistent tumors, nor could it be increased by using serum from rabbits in which tumors had regressed.

The vaccine that has proved effective consisted of processed papilloma tissue mixed with killed bacteria (*Bordetella pertussis*) from a commercial vaccine against whooping cough. The tumor tissue was minced mechanically or treated with trypsin to disperse the cells and then washed with salt water. Vaccines made with either minced or trypsinized tissue were approximately equally effective. Vaccine and virus were administered to test animals.

The percentage of tumors that regressed in vaccinated rabbits ranged from 73 to 82 percent, in contrast to the 30 to 36 percent in unvaccinated animals. This was the only difference in results among vaccinated and unvaccinated animals. For both groups, the interval between virus inoculation and development of tumors, the growth rate of the tumors, and the time of regression were essentially the same.

This work supports the concept that regression of papillomas is mediated by an immune mechanism, thus giving additional impetus to the search for immunological defenses against other forms of cancer in animals and man. (*Nature* 193: 288-289 (1962).)

Induction of lung cancer in hamsters suggests role of agent's physical state

Some investigators believe that the increased frequency of lung cancer in man is due to cigarette smoking or atmospheric pollution, or a combination of both environmental factors. At this time, little is known of the nature of the carcinogen and how it acts. One of the chief obstacles to scientific investigation of this problem has been a scarcity of reproducible methods for inducing the disease in laboratory animals by the route by which substances from the environment enter the lungs of man.

Drs. Katherine M. Herrold and Lucia J. Dunham, Laboratory of Pathology, have reported the successful induction of lung cancer in hamsters by instillation of 3,4-benzpyrene into the tracheobronchial tree. This substance is one of the most potent animal carcinogens so far isolated from either cigarette-smoke condensate or air pollutants. Whether it plays a role in the development of lung cancer in man is still uncertain.

The tumors, some of which histologically resembled squamous-cell carcinoma, a type of bronchogenic carcinoma that occurs in man, were found only in animals that received the carcinogen suspended in Tween 60, a wetting agent. The mucosa of the tracheobronchial tree revealed atypical epithelial changes in addition to the tumors. However, neoplastic lesions were not induced in animals that received the benzpyrene dissolved in olive oil.

The results lead the investigators to suspect that the ability of Tween 60 to increase the permeability of mucous membranes to carcinogens may explain its promoting action and the success in inducing tumors in the present study. It is possible, they believe, that the induction of the tumors was related to the difference in the physical state of the carcinogen—in a suspension rather than a solution. (*Journal of the National Cancer Institute* 28: 467-491 (1962).)

Injections of mineral oil induced plasma-cell tumors in one strain of mice

In the course of laboratory studies of methods of inducing plasma-cell tumors, Dr. Michael Potter and Charlotte Robertson Boyce, Laboratory of Biology, have observed the development of these tumors in BALB/c inbred mice injected intraperitoneally with mineral oil.

These studies are part of a continuing investigation that showed previously the development of plasma-cell tumors in mice injected intraperitoneally with a mixture of incomplete Freund's adjuvants (mineral oil and a wetting agent) and heat-killed staphylococcus cultures.

In the latest experiments, the highest incidence (68 percent) occurred in a group of mice receiving the largest amounts of a commercial grade mineral oil (Bayol F.). Plasma-cell tumors also developed in mice given Primo! D, a purer mineral oil of U.S.P. grade.

Mice given single injections of Bayol F. developed plasma-cell neoplasms as frequently as mice given the adjuvant-staphylococcus mixture.

The report emphasizes that to date tumors have been induced in mice of only one inbred strain. In these experiments, they appear to have arisen from the reactive tissue in the peritoneum. The findings raise the question of whether the injection of a seemingly bland agent, mineral oil, into a suitable place in a particular host, resulting in the development of an unusual type of neoplasm, may constitute a "carcinogenic situation." The investigators suggest that this may have some significance also for man in view of the increasingly widespread use of mineral oil adjuvants in immunological procedures. (Nature 193: 1086-1087 (1962).)

Heavy smokers who move frequently run highest risk of lung cancer

Smokers who move frequently from one community to another are more likely to develop lung cancer than less mobile persons. The risk is greatest for heavy smokers moving from rural areas to metropolitan centers and the foreign-born settling in large cities.

These findings were obtained in a study of lung cancer mortality reported by William Haenszel, Biometry Branch. The investigation was undertaken in an attempt to provide a basis for a better understanding of the causes of lung cancer which annually takes over 39,000 lives in this country. In the study, residence and smoking histories were collected from relatives of a representative sample of the white males who died of lung cancer in the United States during 1958.

Analysis of these data suggests that smokers moving from farm to city or emigrating from their native lands to U.S. metropolitan centers may run a greater risk of lung cancer because their lungs have not had time to adapt to the polluted atmosphere of the new environment.

In general, results of this survey support many earlier studies showing that excessive cigarette smoking is the major factor in the cause of lung cancer. For nonsmokers, residence makes very little difference. On the other hand, the combined effect of excessive smoking and urban residence is even greater than the sum of the two separate risks. (Journal of the National Cancer Institute 28: 947-1001 (1962).)

New publication reports New York State cancer incidence and mortality

The incidence of leukemia, cancer of the lung and bronchus, large intestine, and pancreas increased significantly in both males and females in New York State from 1941-60. In the same period, a significant decrease was reported in cancer of the stomach and buccal cavity in persons of both sexes.

These findings were part of a comprehensive report on cancer trends in New York State, exclusive of New York City, which was published by the New York State Department of Health. The publication, covering about 175,000 cases, presents statistical information collected over the past 20 years by the cancer registry maintained by the State bureau of cancer control.

The death rate from leukemia and cancer of the pancreas and lung increased significantly among both males and females, while mortality from cancer of the stomach and rectum showed a significant decrease. A significant decline also occurred in the uterine cancer death rate, and in male mortality from cancer of the buccal cavity.

Information on the probability of developing cancer, based on the annual average incidence rates for 1942-44, 1949-51, and 1957-59, shows that about one in four males and slightly more than one of every four females can be expected to develop some form of cancer. The probability of developing lung cancer has

risen sharply, and slightly over 3 males in every 100 can be expected to develop cancer of the lung. Breast cancer is responsible for more than one-fifth of the total cancer risk to women: about 6 females in every 100 are expected to develop this type of cancer. (Ferber, B., et al.: "Cancer in New York State, Exclusive of New York City," 1941-60. New York State Department of Health, Albany, N.Y., 379 pp. (1962).)

CHEMOTHERAPY

Acute childhood leukemia responds to treatment with cyclophosphamide

Cyclophosphamide, a member of the class of compounds known as nitrogen mustards, appears to be an important addition to the list of agents useful in the treatment of acute leukemia in children. This finding is revealed in a report of a clinical study conducted under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute. The study was reported by Dr. Donald J. Fernbach, Baylor University College of Medicine.

Forty-four children with advanced acute leukemia participated in the study. Treatment consisted of initial intravenous injection of cyclophosphamide followed by oral maintenance therapy for some of the children, and oral therapy throughout for the others; supportive therapy was administered when indicated.

Eight patients achieved complete remission, and five partial remission, as rated under the standard criteria established for evaluating response to therapy. The complete remissions were independent of previous or concomitant steroid therapy and at the time of reporting had persisted for 3 to 15 months. No cross-resistance was observed between cyclophosphamide and adrenal steroids, 6-mercaptopurine, or methotrexate: every patient who had a complete remission had previously achieved complete remission on a steroid or 6-mercaptopurine, or both, and a complete or partial remission on methotrexate. Cyclophosphamide did not prevent central nervous system complications, which required local therapy for relief.

The most common side effect was low white blood cell count, which was readily reversible by interruption of therapy.

Cyclophosphamide is an alkylating agent that was developed in West Germany in 1957. The synthesis and early laboratory and clinical studies were reported in 1958 by Arnold, Borseaux, Brock, Gross, and others. It is known as B-518 in Europe, is sold there by Asta-Werke under the name of Endoxan, and is marketed in the United States as Cytosan by Meade Johnson & Co., Evansville, Ind. The compound has been studied in the intramural research program of the National Cancer Institute, as well as under the program of the Cancer Chemotherapy National Service Center.

Cyclophosphamide was slightly less effective than the antifolic agent, methotrexate, but more effective than 6-mercaptopurine against advanced mouse leukemia L-1210, and its effectiveness was retained against strains of mouse leukemia which were resistant to antifolic and antipurine agents. In clinical studies, it induced remissions in Hodgkin's disease, lymphosarcoma, and chronic lymphocytic leukemia in adults. (Journal of the American Medical Association 182: 30-37 (1962).)

New plant extract shows activity in patients with acute leukemia, lymphomas

Scientists of the Medicine Branch have reported that vincristine, a new periwinkle plant extract, induces remission in patients with acute lymphocytic leukemia and tumor regressions in patients with Hodgkin's disease and lymphosarcoma. The reports, one by Dr. Myron Karon, the other by Drs. Paul Carbone and Clyde O. Brindley, were given at the 53d annual meeting of the American Association for Cancer Research in Atlantic City.

Vincristine, also known as leurocristine, is available for research purposes from Eli Lilly & Co., Indianapolis, Ind., whose scientists first isolated it. It is the second periwinkle extract found to have anticancer activity. The first was vinblastine, which is useful in treating patients with Hodgkin's disease and a few other forms of cancer.

At the National Cancer Institute, vincristine was given by weekly intravenous injection to 13 children with acute lymphocytic leukemia. Eight, including two who had also received steroids, had complete remissions. Two others had partial remissions. A similar remission rate is usually achieved with methotrexate or 6-mercaptopurine, standard drugs for acute leukemia: the children in this group had become resistant to them.

Five months after treatment with vincristine was begun, 60 percent of the children were still alive. This experience is too limited to indicate how long vincristine-induced remissions may last, but quantitative studies are being conducted under the auspices of the Cancer Chemotherapy National Service Center.

Of 10 patients with Hodgkins' disease given vincristine, tumors regressed completely in four and partially in the other six. The median duration of regression was 1 month. Among seven patients with lymphosarcoma, there were four regressions, three of which were complete. The median duration was 3 months. Only one of five patients with acute myelocytic leukemia had a remission.

Vincristine caused various side effects, depending on the size of the dose. Virtually all patients suffered some hair loss and gastrointestinal disturbances (which could usually be controlled), and many had symptoms of weakness or malaise. Nervous-system disturbances also occurred frequently but usually abated after treatment was stopped. Only in leukemia patients did the drug cause a serious depression in the number of white cells in the blood. This is a therapeutic effect in leukemia, but would have been undesirable in other forms of cancer. (Proceedings of the American Association for Cancer Research 3: 309, 333 (1962).)

New drug induces remissions in adults with acute leukemia

Trials of a new drug by the Medicine Branch have indicated that a new type of compound may prove useful in treating the most common form of acute leukemia in adults. Methylglyoxal-bis-guanylhydrazone, or Methyl GAG, induces remissions in a higher percentage of patients with acute myelocytic leukemia than does any compound hitherto available, but it also causes major side effects. An effort is therefore under way, with support from the Cancer Chemotherapy National Service Center, to synthesize chemically related compounds that, hopefully, will be at least as active but less toxic.

Methyl GAG was originally synthesized and tested in animals by Dr. Frederic A. French, Mt. Zion Hospital, San Francisco. The first clinical studies were conducted at Roswell Park Memorial Institute, Buffalo. The drug is now available from the Cancer Chemotherapy National Service Center for research purposes only.

A report on trials of methyl GAG at the National Cancer Institute was presented at the 53d annual meeting of the American Association for Cancer Research by Drs. Emil J. Freireich and Emil Frei III, Chief of the Medicine Branch. The drug was given by daily intravenous injection to 20 patients with acute myelocytic leukemia. Eleven had complete remissions and two others had partial remissions. The complete remissions have lasted from 1 to more than 8 months; some patients were still in remission at the time the report was presented. Since methyl GAG is ineffective orally, and prolonged intravenous treatment would not have been feasible, patients in remission received maintenance therapy with 6-mercaptopurine (which had been used previously in treating 12 of the patients). Patients in remission were extremely sensitive to 6-mercaptopurine, which affected the bone marrow when as little as 20 percent of the conventional dose was given.

Methyl GAG caused significant side effects in all the patients who had previously been treated with 6-mercaptopurine, but in only three of eight who had not. The major side effect was inflammation of the gastrointestinal tract, but this was usually not progressive, and treatment could be continued at reduced dosage. (Proceedings of the American Association for Cancer Research 3: 319 (1962).)

Experimental methods of enhancing effects of drugs are studied

One of the major goals of basic research in cancer chemotherapy is to separate the anticancer activity of drugs from their adverse effects on normal tissue. Studies of two different experimental approaches to the problem have been reported.

One comes from the Chester Beatty Research Institute in London, where Dr. W. C. J. Ross modified one characteristic of an animal tumor to make it more sensitive to the action of some nitrogen mustards, a family of drugs commonly used in cancer chemotherapy. The rationale was derived from work by other scientists, who demonstrated that neoplastic cells are ordinarily more acidic than are normal cells, and that their acidity is increased by treatment with glucose, a form of sugar.

The London study showed that the antitumor activity of certain nitrogen mustards—those having an affinity for cells whose acidity is relatively high—was enhanced when tumor-bearing animals were given glucose before, with, or after treatment with the drugs. The results also indicated that compounds known as epoxides, which are more reactive than nitrogen mustards under some conditions, might prove even more suitable for exploiting the difference in the acidity of normal and neoplastic cells. The author and his colleagues are investigating this possibility.

In the second study, Drs. S. S. Cardoso and J. J. Jaffe, Yale University School of Medicine, succeeded in enhancing antitumor activity by using combinations of drugs, a technique already employed in treating patients having certain forms of cancer. Their work was an extension of observations made during treatment of leukemia patients with 6-azauridine, which temporarily retards the disease in some cases. The reactions of some patients suggested that the activity of 6-azauridine might have been enhanced by chloramphenicol, an antibiotic given to combat bacterial infections.

The investigators tested combinations of 6-azauridine, in doses too small to have antitumor activity, and chloramphenicol, which has no such activity. The results indicated that chloramphenicol, by an unknown mechanism, enhanced the antitumor activity of 6-azauridine against a lymphoma in mice. The adverse effects of 6-azauridine on normal tissue of the mouse were also increased by the combination treatment. However, this may not present a problem in clinical use, according to the authors, since 6-azauridine has no appreciable toxic effects on man, and, unlike many other anticancer drugs, does not depress the blood-forming function of the bone marrow. (*Biochemical Pharmacology* 8: 235-240; 252-255 (1961).)

Effective drug found for preventing tumor "takes" in laboratory animals

Scientists of the Surgery Branch have reported results of laboratory studies showing that proflavine-hemisulfate, a drug widely used in the treatment of open war wounds, is highly effective in preventing tumor "takes" in wounds seeded with mouse tumor cells.

These studies were part of a continuing investigation by this research group to find ways of improving cancer therapy. Numerous experimental and clinical studies have investigated the possibility that at surgery a wound might be seeded with tumor cells and that these might produce local recurrence of the tumor. A positive correlation between the presence of tumor cells in wound washings and local recurrence has not been established. However, a recent observation that tumor cells were present in the postoperative wound drainage of some cancer patients with negative wound washings made at surgery has stimulated the search for effective tumoricidal agents that could be applied to the operative site.

Two transplantable mouse tumors provided the cells used in the present study. Suspensions of single cells and clumps, simulating the clinical situation, were inoculated into open axillary wounds of mice. Local irrigation with proflavine-hemisulfate 1 to 2 hours after seeding of the wounds was virtually completely effective in preventing tumor "takes." The effectiveness of the drug was markedly reduced if treatment was delayed up to 20 hours and if the wound was made hemorrhagic before the drug was administered.

The study was reported by Drs. Seymour C. Nash, now at Georgetown University Hospital; Alfred S. Ketcham, Chief of the Surgery Branch; and Robert R. Smith, now at Emory University, Atlanta. (*Annals of Surgery* 155: 465-471 (1962).)

BASIC RESEARCH

Immune responsiveness of rabbit cells altered by treatment with RNA

A phenomenon that may open a new approach to overcoming the immunological barriers to transplantation of tissue from one individual to another has been demonstrated by Drs. J. A. Mannick and R. H. Egdahl at the Medical College of Virginia.

Their experiments indicated that ribonucleic acid (RNA) from immune rabbits can modify the immune responsiveness of cells from nonimmunized rabbits. The RNA was obtained from lymphoid cells of a rabbit immunized by skin grafting. (The lymphoid cells mediate an individual's reaction to a graft of foreign tissue.) Lymphoid cells from nonimmunized rabbits were treated with the RNA and then injected into the skin of the rabbit that had donated the skin graft. A positive skin reaction occurred; this reaction paralleled that produced when lymphoid cells from a graft-immunized rabbit were injected into the donor of the graft.

Thus, with respect to the immunological reactivity of the lymphoid cells, the RNA treatment had essentially the same effect as immunization.

Though it remains to be proved, the effect of the RNA treatment may be analogous to bacterial transformation, a process by which nucleic acid transfers hereditary characteristics from one strain of bacteria to another, and to the kinds of changes that occur in cells exposed to nucleic acids from viruses. (Science 137: 976-977 (1962).)

Study provides clue to individuals' different responses to radiation

A laboratory study reported by Dr. Donald P. Doolittle, Roscoe B. Jackson Memorial Laboratory, provides a clue to the observed differences among individuals in their response to radiation. Such information is of fundamental importance to an improved understanding of the mechanisms of radiation damage to living matter in either causing cancer or treating it.

The findings showed that the substitution of a single gene controlling, for example, color or body shape, affected the resistance of mice to radiation. The nature of the effect—that is, increasing or decreasing radioresistance—depended on sex and genetic background. The resistance effects were generally higher in males than females and higher in mature mice than weanlings. Furthermore, the effect of gene changes was apparently not mediated through effects on vigor; differences in resistance were not related to differences in body weight. Resistance to radiation was measured by survival time under daily doses of X-rays. Five inbred strains of mice were used. The substitution of one gene for another in a pair was accomplished by a process of test matings. (Genetics 46: 1501-1509 (1961).)

MENTAL HEALTH ACTIVITIES

WEDNESDAY, MARCH 13, 1963.

WITNESSES

DR. R. H. FELIX, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

GEORGE A. VAN STADEN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF MENTAL HEALTH

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
PUBLIC HEALTH SERVICE			
11 Personnel compensation:			
Permanent positions.....	5,404	7,557	8,633
Positions other than permanent.....	785	617	641
Other personnel compensation.....	115	78	151
Total personnel compensation.....	6,304	8,252	9,425
12 Personnel benefits.....	621	857	939
21 Travel and transportation of persons.....	645	813	941
22 Transportation of things.....	81	95	151
23 Rent, communications, and utilities.....	181	201	326
24 Printing and reproduction.....	56	96	131
25 Other services.....	1,994	3,538	4,100
Payment to National Institutes of Health management fund.....	4,970	5,727	5,883
26 Supplies and materials.....	480	805	882
31 Equipment.....	638	806	918
41 Grants, subsidies, and contributions.....	91,650	121,898	166,287
Subtotal.....	107,620	143,086	189,982
Deduct quarters and subsistence charges.....	1	1	1
Total, Public Health Service.....	107,619	143,085	189,981
ALLOCATION TO ST. ELIZABETHS HOSPITAL			
11 Personnel compensation:			
Permanent positions.....	72	71	71
Positions other than permanent.....		3	3
Other personnel compensation.....	7	5	5
Total personnel compensation.....	79	79	79
12 Personnel benefits.....	6	8	8
23 Rent, communications, and utilities.....	6	23	23
26 Supplies and materials.....	1	4	4
Total, St. Elizabeths Hospital.....	92	115	115
Total obligations.....	107,711	143,200	190,096

Personnel summary

	1962 actual	1963 estimate	1964 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions.....	820	1,113	1,255
Full-time equivalent of other positions.....	111	82	82
Average number of all employees.....	859	1,074	1,182
Number of employees at end of year.....	1,036	1,168	1,306
Average GS grade.....	7.7	8.1	8.1
Average GS salary.....	\$6,798	\$7,401	\$7,464
ALLOCATION TO ST. ELIZARETHS HOSPITAL			
Total number of permanent positions.....	14	14	14
Average number of all employees.....	14	14	14
Number of employees at end of year.....	14	14	14
Average GS grade.....	5.2	4.6	4.6
Average GS salary.....	\$4,990	\$5,313	\$5,313
Average salary of ungraded positions.....	\$5,703	\$5,861	\$5,861

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	42,634	55,635	80,755
(b) Fellowships.....	3,786	5,940	8,534
(c) Training.....	38,608	49,373	66,048
(d) State control programs.....	6,622	10,950	10,950
Total, grants.....	91,650	121,898	166,287
2. Direct operations:			
(a) Research.....	8,822	10,222	10,608
(b) Collaborative studies.....	1,876	3,842	4,363
(c) Training activities.....	282	596	1,001
(d) Professional and technical assistance.....	1,102	2,926	3,998
(e) Review and approval of grants.....	1,908	2,917	3,234
(f) Program direction.....	580	799	605
Total, direct operations.....	14,570	21,302	23,809
Total program costs, funded ¹	106,220	143,200	190,096
Change in selected resources ²	1,491		
Total obligations.....	107,711	143,200	190,096
Financing:			
Comparative transfers to other accounts.....	302	381	
Unobligated balance lapsing.....	825		
New obligational authority.....	108,838	143,581	190,096
New obligational authority:			
Appropriation.....	108,876	143,599	190,096
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (—).....	—38	—18	
Appropriation (adjusted).....	108,838	143,581	190,096

¹ Includes capital outlay as follows: 1962, \$444,000; 1963, \$806,000; 1964, \$869,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$319,000 (1962 adjustments, —\$8,000); 1962, \$1,802,000; 1963, \$1,802,000; 1964, \$1,802,000.**GENERAL STATEMENT**

Mr. FOGARTY. The committee will come to order.

We have before us this morning, the Mental Health Institute, and Dr. Felix, the Director, who has a statement for the committee.

Dr. FELIX. Mr. Chairman, and members of the committee, I have a prepared statement which if you are willing, I would like to submit for the record.

Mr. FOGARTY. All right.

Dr. FELIX. And just summarize some high points.

Mr. FOGARTY. Go ahead.

(The statement follows:)

Mr. Chairman and members of the committee, on this occasion, the 18th consecutive year that I have appeared before you, I should like to describe to you the location and characteristics of today's research and program frontiers in the mental health field. I should like also to indicate where and how the Institute, given your support, plans to move these frontiers forward in the coming years.

For Americans, the term "frontiers" has a very special connotation. It brings to mind our country's past: the forward movement of our Nation from the coastal areas of the Atlantic Ocean to the rocks, cliffs, and forests that fringe the Pacific. But it also carries with it the meaning of "a relatively unexploited field that offers scope for large developmental activity."

As the term relates to mental health activities, I would say that the frontiers exist wherever a new beginning is, or is needed: wherever a beginning built upon all that is good and progressive is being made, and wherever the new beginning is replacing that which is obsolete and repressive.

SYSTEMS OF PATIENT CARE

Thus the frontiers in the mental health field are no further away than the nearest treatment facility, program activity, or research project. And, as in so many other areas of our national life, in the mental health field the old and the new coexist. Our urban renewal projects replace slum dwellings and are surrounded by tenements. In some of our mental hospitals that predate the Civil War, modern research centers and fine clinical facilities can be found a few hundred feet away from buildings—still occupied by patients—that were constructed in the 19th century.

The State hospital

The importance of this dichotomy between the old and the new as it exists in our present system of caring for the mentally ill and mentally retarded cannot be overemphasized. As I have stated over and over again in my previous appearances before you, and as every recent study of the mental health field has confirmed, our primary problem today is that, in the mid-20th century, the walls of the 19th century State hospital—and the system of care enclosed within those walls—still dominate the public aspects of our care of psychiatric patients.

To illustrate:

Eighty-five percent of hospitalized mental patients are in State mental hospitals; nearly half of these patients are in hospitals with populations exceeding 3,000 patients;

Seventy-five percent of these hospitals were opened prior to World War I.

Forty percent of the resident patient population has been hospitalized continuously for 10 years or more; almost 30 percent are 65 years of age or older.

Within these hospitals, on an average, there are 133 patients for every physician; 60 patients for every registered nurse; 6 patients for every psychiatric aid or attendant—in all, 35 personnel per 100 patients. In general hospitals, on an average, there are 226 personnel per 100 patients—seven times as many.

For each resident patient cared for in the various State hospital systems, the cost per day ranges from \$2.11 to \$8.75, with an average cost of \$5.30; in general hospitals, the cost is more than six times as much—\$34.98.

In many hospitals in recent years staff-to-patient ratios have improved and maintenance expenditures have increased. Where this has occurred, these changes have been reflected in better patient care. However, most of our State hospitals still have insufficient numbers of personnel and inadequate financial support. In many hospitals, despite the best efforts of a compassionate but hard-pressed staff, a custodial and repressive atmosphere permeates the whole hospital: an atmosphere expressed in the aimlessness of the patients' daily lives, in the existence—still—of barred windows, locked doors, and seclusion rooms.

Similar conditions exist in the State institutions for the mentally retarded, where, unlike the State mental hospitals whose resident population has decreased

in recent years, the number of patients has increased steadily since 1946 at the rate of 2.5 percent per year.

As stated in the final report of the Joint Commission on Mental Illness and Health:

"It does not require further analysis to conclude that patients in State and local governmental hospitals fare the worst of any type of hospitalized patient in the country, as judged by the significant indices of available money and available personnel. This has always been so, and 'recent progress' has not changed the fact."

However, I am not here today to emphasize the negative aspects of this statement or of the traditional State hospital. My concern, rather, is to emphasize that it is here a new beginning must be made—a beginning that will do away, eventually, with present obsolete and repressive features.

Community treatment facilities

However, the State hospital is not the only mental health frontier concerned with patient care. On the positive side there are at present several significant trends and goals on which to build for the future. Custodial approaches are being replaced by therapeutic measures. Treatment efforts are directed toward minimizing the patient's defects and emphasizing his assets. A growing expression of the newer therapeutic approach is found in the change in concept from isolating the patient from the community for treatment purposes, to preserving the patient's links with the community, thus capitalizing on the community therapeutic effects.

The frontier that needs changing exists in the State hospital. The frontier that offers "a relatively unexploited field for large developmental activity" exists in the community, where increasing numbers of the mentally ill are being cared for by modern treatment methods that reflect our present state of psychiatric knowledge and skill.

I am speaking now of outpatient psychiatric clinics, and of the increasing availability of psychiatric care in the short-term, community general hospitals. For example, in 1961, for every 100 patients cared for in State hospitals, 86 were served in the country's 1,500-plus psychiatric outpatient clinics. In addition, in 1959, the last year for which figures have been analyzed, 147,500 psychiatric patients who had been cared for in general hospitals were discharged to the community. That is 15,000 more than were admitted that year to public mental hospitals for the first time.

To those of us who have spent our entire professional lifetime in trying to improve the care of the mentally ill, these statistics carry with them great significance and a tremendous sense of excitement. They indicate that a large proportion of the mentally ill can be treated and cared for in the community—thus retaining their place in society. They validate our hope and belief that the great breakthrough in our mental health programs has already occurred—a breakthrough that will eventually demolish the walls of the traditional State hospital. In its place a system of care for all mental patients except the severely, chronically ill will be built within the community.

Nor is the increased availability of psychiatric care in general hospitals and outpatient clinics the only indication we have that care of the mental patient in the community is effective, practical, and inevitable. The final reports of research and demonstration projects undertaken with the support of National Institute of Mental Health funds abound with such evidence.

In one such study, which extended over a 5-year period of time, schizophrenic patients previously hospitalized in a State hospital were given continued drug therapy and psychotherapy in an aftercare clinic. Many of these patients had been hospitalized from 2 to 13 years. However, with aftercare, only 10 percent of such patients required additional hospitalization—a considerable reduction in the expected return rate of such patients.

In addition, the study indicated that when such patients do experience a recurrence of overt psychotic symptoms, their symptoms may be brought under control in 2 to 4 weeks by treatment in a day hospital. If, on the other hand, patients are returned to the State hospital when their symptoms reappear, treatment is likely to extend from 3 to 12 months—and occasionally longer.

Comprehensive mental health programs

The results of this and other studies, plus the proved effectiveness of treatment in the community, have led us to the conviction that patient care of the future must be guided by the following three principles:

1. Mental patients are similar to patients suffering from a physical disorder in that they may require a variety of therapeutic measures and facilities during the course of their illness.

2. "Patient care" includes the concept of the prevention of severe and long-term disablement through early diagnosis and treatment.

3. The primary goal of treatment should be the prompt return of the patient to a productive role in society.

We believe that measures designed to implement these three principles concerned with patient care and treatment and to protect and promote the mental health of our citizens will take the form of comprehensive community mental health programs.

We conceptualize such a program as embracing the following:

One area, which includes the bulk of present mental health services, is concerned with early diagnosis and prompt treatment of mental and emotional disorders and with mental retardation. This embraces all of the various clinical services that are available: The therapeutic skills provided not only by the psychiatrists practicing in the community, but those of other physicians as well; outpatient facilities, psychiatric and others; psychiatric services in general hospitals; specialized psychiatric institutions. Essential also are the case-finding services provided by schools, welfare agencies, and public health departments.

A second essential area includes followup and rehabilitative services for persons returned from inpatient care, or for those in foster homes or similar care.

A third component of a comprehensive mental health program is the provision of consultant services to schools, courts, public and private health and welfare agencies, and the other help-giving agencies in the community. Such consultation enables professionally trained people in the community to incorporate mental health principles and practices in their everyday relationships and work with their clients.

A fourth essential is public education. This includes public information and education programs which utilize the mass media, as well as educational activities conducted in small groups.

A fifth component of a community mental health program is program and operations research—research to find answers to those community problems that are associated with the mental and emotional disorders, and to try out and evaluate the effectiveness of new or unique mental health programs designed to meet the needs of a community.

A sixth essential component of a comprehensive community mental health program involves efforts to prevent mental illness. From the standpoint of public health, this is in many ways the most important element of all. Prevention of mental illness implies not only the reduction of those factors which tend to produce mental and emotional disturbances, but also the provision of a climate in which each citizen has optimum opportunities for responsible participation in the life of the community, and for the development of his particular potentialities.

Unlike the State hospital system—which must be changed—or our system of community treatment facilities—which must be further developed—the three principles of patient care which I have outlined—plus the six components essential to a comprehensive community mental health program—exist today primarily as an advanced area of thought. Noble and fruitful attempts are being made in many parts of our country to provide for the continuous and comprehensive care of the mentally ill, and to build comprehensive community programs. However, to my knowledge, there is not now in existence a single comprehensive community program that embodies all six essential components, or that provides for the continuous and comprehensive care of more than a fraction of the mentally ill and mentally retarded persons in the community.

Therefore, it is primarily to these ends that the National Institute of Mental Health is planning its program for this year and the coming years: that the State hospital and institutions for the retarded be revamped, that community treatment facilities be further developed, and that comprehensive community programs come into being.

Hospital demonstration grants

Thus we plan—and provision is made for this in the budget before you—to initiate a program of hospital demonstration grants to upgrade the level of patient care in the Nation's State hospitals and institutions for the mentally disabled.

Obviously, a major new effort is needed to stimulate every State hospital and institution in the Nation to better its services. A \$12-million expansion of mental health project grant funds this year, as part of a 3-year plan to reach every State institution for the mentally disabled, will initiate an all-out effort to revamp the State hospital system.

If these funds are appropriated, it is proposed that the staff of National Institute of Mental Health will encourage the State authorities to develop plans for program demonstrations. It would be planned that such demonstrations would begin in one-third of the institutions this year, with the provision that there would be at least one such demonstration in each State. Demonstrations in the remaining two-thirds of the institutions would be established in the next 2 successive years. Applications for the support of hospital demonstration projects will be reviewed by a special committee of experts well acquainted with hospital problems and programs, and by the National Advisory Mental Health Council.

Making this program available to every State hospital and using the consultant staff of the National Institute of Mental Health to stimulate its implementation would actively meet an urgent mental health need present in every State and territory. Individual hospitals and institutions would be enabled to develop projects to—

1. Organize special programs for the alcoholics, and the geriatric mentally ill.
2. Set up units for emotionally disturbed children.
3. Set up screening and diagnostic units in institutions for the mentally retarded, to prevent, wherever possible, the institutionalization of the mentally retarded.
4. Explore new and more productive ways to use auxiliary personnel such as psychiatric aids, practical nurses, college students, social work aids, and volunteers.
5. Develop predischARGE programs to prepare the families and employers of the patients, as well as their home communities, for their return to a productive life at home.

Such projects, we believe, will stimulate new planning, implement the development of operations research and program evaluation, encourage the exploration and development of new patterns of care, and thus transfuse the staff and patients with new hope and new ideas.

Regular community programs

Such is the special new program concerned with the upgrading and improvement of the State hospital system that we expect to initiate in 1964, given your support. It is anticipated that this new program will be launched without in any way compromising the effectiveness of existing programs of assistance, or interfering with their expansion when such expansion is appropriate.

Moving now from this exciting new program of hospital demonstration grants, I would like to summarize briefly for you recent developments in our existing programs as they relate to the care of the mentally ill and the promotion of mental health in the community.

First, we have taken a number of steps to increase the effectiveness of professional and technical assistance to the State mental health authorities, and to other groups and agencies working in the field of mental health.

Specifically, the following developments are worthy of noting here:

(1) The scope of our demonstration program has been greatly enlarged in an effort to accelerate the translation of research findings into mental health program operations. Demonstrations are now underway concerned with the control of phenylketonuria (PKU), with the control of narcotics addiction in the community, with an information and counseling service for families of the mentally retarded, with the treatment and rehabilitation of alcoholics in the community, and with the effective utilization of recent research findings concerned with the behavioral disturbance of children in ordinary classrooms.

(2) Forty-seven projects designed to give technical assistance to mental health and other program personnel were held in 28 different States, by far the largest number held in any one year. Some indication of the total national impact of these projects, designed to promote the utilization of the latest research and program information, can be derived from an examination of the kinds of people who attended technical assistance projects as participants. These included: clergymen, child welfare workers, law enforcement officers, attorneys, youth court judges and counselors, executives and casework super-

visors in family service agencies, State legislators, superintendents of public schools, representatives of mental health training institutions, and of the major mental health professions.

To summarize: Through a new program of hospital demonstration grants, and through increasing the effectiveness of our regular programs of consultation and technical assistance, the Institute next year and in the coming years is looking forward to the achievement of three goals: The upgrading of the State hospital system, the development of community treatment facilities, and the establishment of comprehensive community mental health programs.

TRAINING PROGRAMS

Central to any effort to renew or develop these frontiers is the need to provide additional trained manpower to do the job. The Joint Commission report points out that "sufficient professional personnel to eliminate the glaring deficiencies in our care of mental patients will never become available if the present population trend continues without a commensurate increase in the recruitment and training of mental health manpower."

The documentation of a shortage of trained mental health manpower in the four core professions has already been made by the Joint Commission. It is important to note that this shortage exists despite the fact that there has been a sizable increase in the numbers of trained professional workers in the core mental health professions between 1950 and 1961. Altogether, in the fields of clinical psychology, psychiatric nursing, psychiatric social work and psychiatry, there has been an increase from a total of approximately 12,000 with recognized graduate training in 1950 to a total of approximately 29,500 in 1961. This increase of almost two and one-half times is a dramatic indication of the acute manpower shortages that existed in mental health in 1950, as well as a testimony to the effectiveness of the training programs and their potential for the future.

The production of needed trained personnel in the core mental health fields, however, is not the total story. As new concepts of treatment and research and teaching in the field of mental health have emerged, new needs for a wide variety of mental health skills have become apparent, and the program has therefore extended much beyond its original scope.

Thus, from the beginning of the program through the middle 1950's, the major emphasis was on graduate training for clinical service in the core professions. More recently, there has been increased emphasis on support for research training in all fields of relevance to mental health.

Current programs

Grants are now provided not only for clinical and research training in the four core professions but also for (1) relevant research training in the biological and social sciences; (2) mental health training in schools of public health; (3) pilot projects in incorporating mental health concepts in the training of lawyers, educators, clergymen, and other groups, and to training in special areas such as aging, mental retardation, and juvenile delinquency; (4) training general practitioners to play a more effective role in psychiatric treatment; (5) programs in medical schools leading toward the integration of the behavioral sciences into the education of the modern physician; (6) special projects to support conferences, institutes, workshops, and surveys of relevance to mental health training.

The Institute's training program has grown significantly since 1948. From 1948 through 1961, approximately 12,000 persons received graduate trainee stipends; and additional thousands received training in mental health concepts and skills in undergraduate programs in psychiatry and psychiatric nursing, and in training programs for general practitioners, and so forth.

Future developments

We now are looking forward to still another new development in the Institute's training program. As determined efforts are made to improve the treatment programs in the hospital and community, it will become increasingly important to provide a wide variety of training opportunities to all levels of personnel actually employed in service settings. This includes not only the hospital and the research center but also general hospitals, community outpatient clinics, schools and hospitals for the mentally retarded, and programs concerned with aftercare and rehabilitation services.

Further development in the Institute's training program will therefore be directed toward the following goals:

1. First and most important, inservice training opportunities must be provided to all levels of personnel working in all types of mental health settings. Such training might be accomplished by a variety of short-term programs, either on the job or at formal training centers. Personnel to be so trained include administrators; the professional personnel providing treatment; and allied personnel such as occupational therapists, physical therapists, aids, and attendants.

2. Developmental training grants should be provided to State mental health authorities to help State and local mental health programs improve their services through orientation-for-the-job training, inservice training, continuation education, and other staff development activities.

3. Existing graduate and undergraduate programs in the core mental health fields must be strengthened and expanded.

4. Research training must be extended not only in the mental health professions, but also in the relevant biological and social sciences.

5. Training for work in special areas such as mental retardation, juvenile delinquency, aging, and alcoholism must be expanded.

6. Training in mental health concepts and techniques must be further extended to nonpsychiatric physicians who play an important role in providing preventive and treatment services to the mentally ill or to patients whose illnesses have an emotional component.

7. Training programs must be expanded in the areas of public health, community mental health, and preventive services.

8. New teaching and training methods must be devised to make the communication of new knowledge more effective, and to apply this knowledge to clinical problems.

9. Since information concerning the supply, demand, deployment, and utilization of manpower will be crucial in future program planning, comprehensive efforts should be and are being made to obtain more information about mental health manpower.

10. Projects to improve recruitment efforts should be initiated to insure that an appropriate number and quality of students seek training in the mental health field.

Mr. Chairman, I would like to emphasize at this time the fact that, to a large extent, it is upon the success of the Institute's training program that the Institute's other programs depend. If we are to do away with what is repressive in our State hospital systems, if we are to make available more treatment facilities in our communities, and if we are to develop comprehensive community mental health programs, we must make, in the coming years, an all-out training effort.

RESEARCH PROGRAM

Equally critical is our need for research in the diversified areas involved in mental health.

As Dr. Seymour Kety has said:

"There are well-ordered master plans in other branches of science, whose boulevards are already laid down, the trees pruned and the hedges clipped, and whose byways and alleys, even where they have not been broken through, have at least been indicated. In comparison with these, the territory of psychiatry is largely uncharted and unexplored, or spotted by primitive settlements trying to cut paths through the jungle between them. A creditable list of mental disorders have yielded their secrets to the pathologist or to the chemist; but the major psychoses taunt us today as they did the Hippocratic physicians."

Why is the territory of psychiatry largely unexplored or spotted by "primitive settlements"? Dr. Kety answered this question in part when he said:

"In the case of the brain, the biological disciplines have made and will continue to make remarkable progress toward understanding its structure, its metabolism, its functional interrelationships, and the mechanisms which underlie behavior. They have solved or will solve those mental disturbances which are primarily the result of disturbances there. But in the area of information, content, and experience, stored as it is in the complex interrelationships of 13 billion neurons, biology is extremely pretentious if it thinks it can unravel them by means of its tools.

It has become increasingly evident that a broad attack is needed, utilizing many disciplines, if we are to unravel the causes of mental illness. Nowhere in our program is this broad attack better illustrated than in the area of

schizophrenia. Consonant with the scope of the problem, schizophrenia research encompasses a variety of sciences—including medical, biological, psychological, and social. Clues to prevention and etiology and treatment are being sought in the chemistry of the body as well as in the quality of the mother-child relationship; in the mechanism of the brain along with the social structure of the community; in the effects of psychoactive drugs and the dynamics of the patient-therapist relationship. The contributions of the biochemist merge with those of the pharmacologist, the findings of the anthropologist with those of the social psychologists; and often, members of highly divergent disciplines work together as members of a single research team.

The fields of study encompassed range from the most molecular of the biological sciences to the broadest of the behavioral sciences. Over one-third of the studies of schizophrenia supported by the Institute this past year were in the area of clinical psychiatry, one-fourth in the areas of psychology—clinical, physiological, social, and educational. Other studies spanned such areas as psychopharmacology, biochemistry, physiology, anthropology, sociology, public health, and hospital administration.

Behavioral sciences

You will note that much of the research program falls within the area of the behavioral sciences.

These sciences, being comparatively young, form a major research frontier. Being young, they have not yet achieved the acceptance in the public mind accorded the physical and biological sciences.

I should like, therefore, to discuss briefly some of their characteristics and their relationship to mental health problems. For the former, let me summarize some of the highlights of the statement on the behavioral sciences issued last April by the President's Science Advisory Committee.

This statement delineated some basic characteristics of the behavioral sciences. One is utilization of the traditional scientific process whereby observation, experimentation, and exhaustive exploration come into play as the scientist pursues, develops and modifies a working hypothesis. Another is the cross-fertilization process, in which scientific fields diverse in subject and in stage of development share in the continuing free circulation of ideas and concepts, and the development of new scientific techniques.

On the one hand the behavioral sciences are characterized by laboratory experiments. On the other, by observation of what occurs often in a natural setting without intervention. There is a clear-cut division between these methods; yet neither is fully effective without the other.

We have here a field where the unsolved problems, no longer minor or trivial, are clearly solvable; and where methods of attack are already in the hands of scientists. It is a field that deals with problems of tremendous scope, and of steadily increasing scientific importance.

As the behavioral sciences relate to mental health, they may be defined as the study of behavior of intact organisms, using techniques that provide systematic and verifiable data about variables related to the health and illness of human beings. Their specific relevance to mental health problems is further emphasized when we consider that the phenomena of the mental disorders make themselves known primarily through behavior.

Such research serves to meet the needs of the program most directly as it clarifies the role of psychological and social factors known to be important in the etiology, prevention, and treatment of mental and emotional disorders; or as it advances attempts to identify additional variables related to mental illnesses, and to improve techniques for measuring them.

Studies of a more basic sort, in which investigators seek to increase our fund of knowledge about basic social and behavioral processes themselves, are essential to a mental health research program.

In further elucidation of the diversity of research being conducted by the National Institute of Mental Health, it is of interest to note that last year more than 30 professional disciplines were represented among the scientists receiving grant awards. The program spanned more than 35 scientific fields of study. More than 20 different types of academic departments were associated with those projects sponsored by colleges and universities and 34 different NIH study sections and committees were assigned NIMH grant applications for review. Among major areas of health and social problems being investigated, besides schizophrenia, were mental retardation, juvenile delinquency, alcoholism, drug addiction, aging, psychopharmacology, and child

personality and development. In the pursuit of biological and biochemical factors related to mental illnesses, neurobiologists, neuropharmacologists, biochemists, physiologists, microbiologists, and biophysicists are pushing forward on many fronts, and many new and exciting clues have been revealed.

We have not solved the yet inscrutable mystery of the major psychoses. But it has become apparent that the causes of mental disorders may reside in genetic factors, and metabolic errors, and psychological stresses, and social experience; and that two, or more, of these factors may be involved in any clinical problem. In view of this, we must continue as we now are—working on all these fronts. We have closed out some possibilities and disproved some old assumptions. We have developed new questions—and new methods. This effort, growing every year, will result, I am convinced, in achievements that will rank with the greatest of those in any health field.

POLITICAL AND SOCIAL DEVELOPMENTS

Mr. Chairman, I have tried to review for you some of the more important research and program frontiers in mental health. In conclusion, I would like to bring to your attention certain recent developments related to mental health that are of significant implication.

This committee and the Congress of the United States have amply demonstrated their profound concern with this area. It was from this committee that there emerged in 1955 the recommendations for congressional legislation that resulted in the initiation of the study by the Joint Commission on Mental Illness and Health, designed to survey needs in this field and develop a program for action.

All of you well know the tremendous repercussions that have ensued from the publication, in the spring of 1961, of the Commission's final report, aptly entitled "Action for Mental Health." The interest and concern it has engendered in communities throughout the land, and the ferment it has aroused regarding the need for action in mental health, are already a matter of history.

The report has been summarized and discussed by groups, professional and lay, in hundreds of communities; by State legislatures; and recommendations ensuing from the report's findings have been drawn up by the Governors of the States.

The National Association for Mental Health last spring convened 300 leaders of the major national organizations interested in mental health and mental retardation to discuss what the voluntary citizen organizations could do to implement the findings of the Joint Commission report. And this past fall the American Medical Association held a National Congress on Mental Illness and Health, at which the AMA pledged its determined intent to throw its resources into the fight against mental illness.

The 87th Congress expressed its concern for the need for action by earmarking new funds for State planning as a start on strengthening community mental health services.

The President has indicated his keen awareness of the need for action in mental health by appointing a Cabinet-level Committee to review the recommendations of the report and develop proposals for appropriate Federal action.

The results of the Committee's deliberations, and the findings and recommendations of the President's Panel on Mental Retardation, were submitted to the President in the fall of 1962. The views of the President are reflected in the budget request before you, and were further delineated in his special message on mental illness and mental retardation.

As he stated then, "For too long the shabby treatment of the * * * mentally disabled in custodial institutions and the many millions more now in communities needing help has been justified on grounds of inadequate funds, further studies, and future promises. We can procrastinate no more."

The broad programs of action to combat mental illness, contained in the special message, are focused on comprehensive community mental health centers to be established across the country. Thus his first recommendation to Congress was for authorization of grants to the States for construction of comprehensive community mental health centers, beginning in fiscal year 1965, with the Federal Government providing 45 to 75 percent of the project cost. The second recommendation that relates to the community mental health centers is for authorization of short-term project grants for the initial staffing costs of comprehensive community mental health centers, with the Federal Government providing

up to 75 percent of the cost in the early months, on a gradually declining basis, terminating such support for a project within slightly over 4 years.

I submit that these unprecedented activities in the area of political and social action which have occurred during this past year mark a breakthrough of no less significance than the breakthroughs I have discussed earlier—which have opened the way to the eventual demolition of the traditional State hospital, and laid the foundations for care within the community for all but the severely chronically ill.

I firmly believe that the actions of this Congress and this administration will determine whether we are to conquer the scourge of mental illness and mental retardation in our generation or leave it to those who follow after us in another time and another century.

With so much of the strength of this country pledged to move forward, I cannot see how we can fail.

The request for 1964 is \$190,096,000 as compared with an operating level in 1963 of \$143,200,000. There is an increase of \$46,896,000 which is spread among the activities of the Institute for ongoing programs and for implementation of recommendation stemming from the Joint Commission report and in the report of the President's Panel on Mental Retardation. These increases are discussed in detail in the budget justification. The request for 1964 is distributed as follows:

Grants:

Research-----	\$80,755,000
Fellowships-----	8,534,000
Training-----	66,048,000
State control programs-----	10,950,000
Subtotal grants-----	166,287,000

Direct operations:

Research-----	10,608,000
Collaborative studies-----	4,363,000
Training activities-----	1,001,000
Professional and technical assistance-----	3,998,000
Review and approval of grants-----	3,234,000
Program direction-----	605,000
Subtotal direct operations-----	23,809,000
Total 1964 appropriation request-----	190,096,000

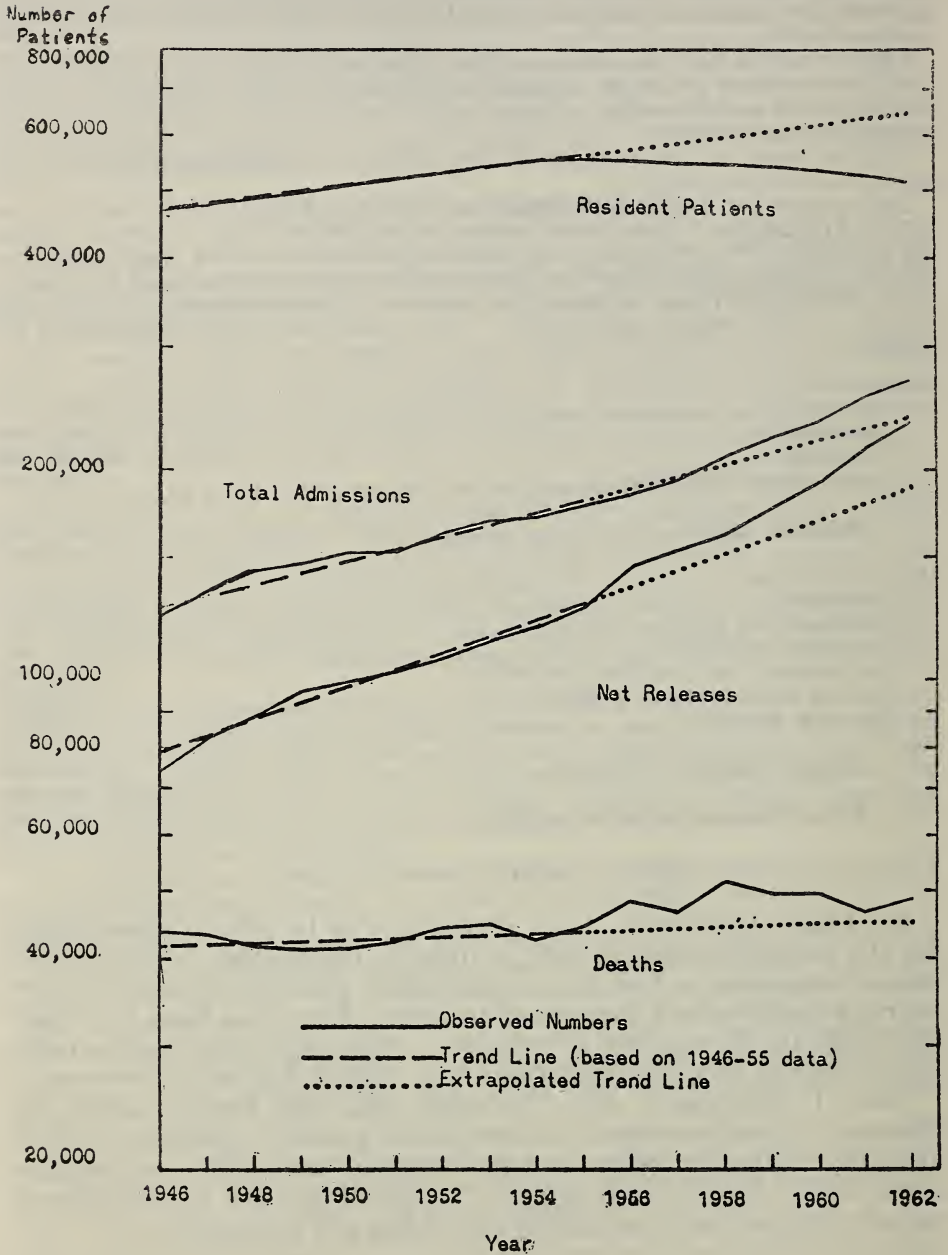
DROP IN HOSPITALIZED PATIENTS

Dr. FELIX. Gentlemen, I am very happy to be able to report again for the seventh successive year, a drop in the number of patients in mental hospitals; in fact, the largest single year's drop since the first year the trend turned downward in 1956. There has been a 2.2 per cent drop in the number of patients. The total drop, incidentally, since 1956 the first year that there was a drop, has been 8 percent.

Now, I understand, Mr. Chairman, that Mr. Denton asked Dr. Shannon a question about this decrease in patient population, and in anticipation that he might, and the others of you might wish to know about this, I have a chart which I would, if you are willing, like to submit for the record, and tell you a thing or two about it.

(The chart follows:)

NUMBER OF RESIDENT PATIENTS, TOTAL ADMISSIONS, NET RELEASES, AND DEATHS, AND EXTRAPOLATED TREND LINES (BASED ON THE YEARS 1946-1955), PUBLIC MENTAL HOSPITALS, UNITED STATES, 1946-62



Source: Data collected in annual census of patients in mental institutions, National Institute of Mental Health.

Had the 1946-55 trend in the resident patient population continued, there would have been almost 650,000 resident patients by the end of 1962. However, the resident patient population has declined since 1955 at an average rate of 1.1 percent per year. The observed resident patient population at the end of 1962 was only 515,948 as compared with 650,000, a drop of 134,052. This has resulted in a substantial accumulated saving in maintenance costs during the 7-year period 1956-62, which is estimated conservatively to be \$700 million.

Dr. FELIX. You will notice on this chart, looking at the top line particularly, a dotted line, that is going up at an angle, and then a solid line below it which slopes downward. The solid line represents the number of patients actually in the hospital in the various years, which you will notice indicated at the bottom of the chart. The dotted line is the trend of the projected patient load, based upon an 11-year experience, from 1946 to 1955.

Now, had the patient population increased as it had been projected originally, there would have been, by the end of calendar 1962, approximately 648,000 patients. Actually, there were 515,948 or in round figures, 132,000 patients less than the anticipated number.

MONETARY SAVINGS RESULTING FROM REDUCTION IN NUMBER OF MENTAL PATIENTS

Now, this number of patients, had they been in the hospital, in the various years, at the cost per patient for those years, would have cost the public about \$700 million. There is this much money that was not spent for patients who were not there, who had been predicted would be there, according to this 11-year trend.

Now, this amount I might tell you, is greater than the total amount of money expended on State and local public mental hospitals in 1956 (approximately \$619 million). Or, you might also be interested to know that this is greater than the total amount of money appropriated to the National Institute of Mental Health since it was organized in 1948 (approximately \$678.5 million). The money saved by these patients not being in the hospitals, is greater than the total amount of money that Congress has appropriated for the operation of the National Institute of Mental Health for grants for research and training, and for all other purposes.

This \$700 million, however, is only part of what has been saved. There were 559,000 patients in the hospitals the last peak year, which was 1955. You may remember that during that and preceding years, I had told you that these hospitals were overcrowded. They were bursting at the seams, and many beds were obsolete. They would need replacing.

Not counting replacement, but just providing space for these new patients, would have meant the erection of about 89,000 additional beds in State and local mental hospitals.

Now, the Hill-Burton people tell me that the cost for construction has averaged about \$15,000 a bed. This would mean that, by not having to build these 89,000 beds, we have saved an additional \$1,300 million. So the savings in maintenance of patients plus the savings in construction come to about \$2 billion, which has been saved since 1956.

This, I might say, is not much less than the total amount of money spent in 1961 for maintenance and care of patients, including veterans'

pensions and including our best estimate of private expenditures for patients in private hospitals and clinics, and by private physicians (\$2.1 billion). I use 1961 since it is the last year for which we have complete figures.

This, in reply to Mr. Denton's question, is the best estimate we have of the savings to date—about \$2 billion.

Now, the population, as I have said, has dropped.

ROLE OF INSTITUTE IN IMPROVED STATUS OF MENTAL HEALTH

Mr. FOGARTY. Before you get any further, Doctor, why don't you explain the Institute's role in this area, leading up to this downward trend?

Dr. FELIX. You may remember sir, that the objectives of the Institute are the training of personnel to meet needs not only for research but for manning of hospitals and clinics, the support of research bearing on mental illness and health, and the development of extramural mental health facilities. The number of personnel in these hospitals has increased, and very significantly so, due to training programs of cant part from the development of the new psychoactive drugs, which have been stimulated in significant part by the training program of the National Institute of Mental Health.

In addition to this, there have been developed a number of new techniques—treatment techniques—which have proceeded in significant part from the development of the new psychoactive drugs, which have made possible the release of patients earlier; the maintenance of patients in extramural facilities, many of whom can now be treated and kept at home, so that it is no longer necessary to place them in hospitals.

Now, as this has gone along, there has been a decrease—

DOLLAR SAVINGS FROM DECREASE IN NUMBER OF PATIENTS

Mr. DENTON. There is one thing I want to say about these savings. Of course, many of these people who are released from the hospital are making money now and paying taxes.

Dr. FELIX. That is true, sir.

Mr. DENTON. The Government is making money, so there would be more than that \$2 billion.

Dr. FELIX. That is true, sir. I do not have the figures with me but we have calculated this. We have asked an economist to do some figuring on it. If half of these people—let's see, this is for any 1 year—if half of these people were paying taxes at the average rate—I forget what it is, but there would have been an increase in Federal and State and local tax revenue of somewhere near \$300 million. This is in addition to the \$2 billion. This is due to—I don't know enough about economics to know how you do it exactly—but this is based on the observation that, as the gross national product increases by a certain amount, there is a certain proportion of it that goes into taxes, and these people would be working, thereby increasing the gross national product.

Dr. SHANNON. Dr. Felix has put these figures on an annual rather than an aggregate basis. I think the annual data might be more

meaningful because the savings have been increasing annually as a part of an 8-percent drop in patient population since 1956. I think the annual figures are highly significant. I have done some pencil calculations, here, and I think the data becomes even more impressive if one can project them, rather than dealing with what has been saved in the past.

Dr. FELIX. Yes; that is true. Yes, sir.

ROLE PLAYED BY TITLE V PROGRAM

The passage of what we call the title V program—the passage of the legislation which authorized the title V program now called section 303, Public Health Service Act, made possible an expansion and extension of our demonstration and research efforts in the area of care and treatment of patients both in and out of hospitals. This has resulted in the development of new techniques; such things, for instance, as the actual treatment of psychotic patients—nondangerous psychotic patients—in outpatient or in office practice, rather than requiring that they go to a hospital.

All of these things, acting together, have turned the tide, and as I bring out, I hope successfully, a little later, we have reached the point now where we are ready to move into a much enlarged program.

The Congress has appropriated funds over the years to tool up. We are toolled up, we have the people, we have the motivation, we have the know-how to begin, we are ready to go.

PATIENT AGE GROUPS DIFFER

A few more facts about these patients might be helpful.

It is interesting that the age group which has shown the greatest drop over the years, among the hospital population, is that which earns the most money—the age group 35 to 44. They have dropped at the rate of 3 percent per year to put it another way; a total of about 18,000 less are in the hospital than there were when the drop began. All other age groups have shown some drop with the exception of two, and this gives me real worry. I cannot tell you why, exactly, but I think we must study more intensively these two groups. These groups are the ones from 15 to 24, which has shown an annual increase of 4 percent, and the group under 15, which has shown an annual increase of 14 percent. The number of patients under 15 in public mental hospitals today is almost twice what it was in 1956, the first year that this trend turned downward.

The reason this has not made a significant impact on the total figures is that the total number is relatively small. I think it is about 4,000 now, but I don't like this rate. I don't know why it is occurring. I hope I will be able to report why before too long, because we are working energetically at this. It gives me real concern.

TREATMENT AT GENERAL HOSPITALS

Now, one of the reasons that the hospital population has been able to drop off has been the development of psychiatric programs in general hospitals. A number of hospitals have beds for psychiatric patients now. This has increased.

In 1960 there were 198,000 psychiatric patients admitted to general hospitals. This compares to 140,000 first admissions to public mental hospitals and is almost as much as the 225,000 total admissions to public mental hospitals.

Now, this is where a lot of patients have gone who formerly went to the mental hospital, and because of this there has been a reduction in the number of beds.

California reports a 33-percent reduction in the rate of occupancy of beds since 1950.

Worcester, Mass., State Hospital, since 1957, has lost 41 percent of its hospital population. It is that much smaller than it was.

Of these patients who go to general hospitals, about 75 percent return directly to their homes. They do not go to any other hospital, public or private.

There are now about 600 general hospitals with psychiatric services. Twenty years ago, there were about 40. The average patient's stay varies from 23 to 33 days, in such representative cities as Sacramento, Louisville, Hartford, Ann Arbor, Philadelphia, Dallas, or Washington, D.C.

This is a short enough period of time so that the illness is insurable. As soon as it becomes insurable, and people's insurance covers such illnesses, people will apply for help earlier, because it no longer becomes financially catastrophic to do so. There are funds to cover the needed treatment. This means earlier attention, and very likely, most probably, shorter treatment in a great majority of cases; quicker return to work. So we are in a salubrious spiral here, it seems to me, as each thing that happens makes it easier for the next good thing to happen.

I reported in the past about the experience in Georgia, where there were four; there are now seven general hospitals which accept psychiatric patients.

An interesting program is that at the Malcolm Bliss Hospital in St. Louis where they have developed a rather high ratio of doctors to patients, but by so doing, were able to reduce the average stay of patients to 31 days. Now, their per diem cost is \$24 or a cost of about \$744 to hospitalize, and treat a patient, to the point of discharge.

The State hospital per diem is \$4.43 as opposed to \$24, but the average stay there is 225 days or the cost per patient is \$997. There is an actual dollar saving then, in increasing the per diem cost, so long as this means increased quality and quantity of services to patients. This is one of the things that we are now pushing as hard as we can.

OUTPATIENT CLINICS

Of course, another reason for the reduction in patient load in the mental hospitals has been increase in outpatient clinics.

There were over 1,650 outpatient clinics in 1962, as compared to only 500 in 1946, the year the Mental Health Act was passed.

The great bulk of these were developed due to assistance through the grant-in-aid funds from the National Institute of Mental Health, made possible by appropriation.

There were 665,000 patients seen in outpatient clinics in 1961. An interesting thing here is that there were 100,000 psychotic patients

seen; this is 45 percent more than there were in 1955. Also, we are developing now, emergency psychiatric services, around the clock, 24 hours a day, where one can get emergency attention. Brooklyn, N.Y., in Kings County Hospital, saw 400 such emergencies last year. Berkeley, Calif., has such a program. The Detroit Receiving Hospital's children emergency psychiatric service sees these patients and reports that 6 percent of the children that they saw in emergency last year were suicidal or true suicidal attempts.

Twenty-eight States now have day and night hospitals, and nine other States are planning such programs, which will allow day hospital care; another patient can occupy the same space for night care, and go home in the day.

Homemaker services are developing. North Carolina and Pennsylvania have them, and the Evansville, Ind., State hospital has a mental health project grant from the National Institute of Mental Health to demonstrate the unique merits of the homemaker services as an integral part of the State hospital's program. It is apparently reducing the length of stay of patients who are eligible for this type of treatment.

Illinois—the Department of Mental Health of the State of Illinois has made a grant out of their funds, to study this program in that State.

IMPROVED MANPOWER SITUATION

The manpower situation is improving.

In 1950, I reported to you that the number of psychologists, nurses, social workers, and psychiatrists, working in the field of mental health were about 23,000. This increased to 44,200 by 1960, and I have just received a report before I came here this morning, that as of—I think it is the first of this month, in 1963—there are 51,000.

Our plans are, with your approval and assistance, to double that 1960 figure by 1970. This is part of the plan which will permit us to cut the number of patients in public mental hospitals to somewhere near 50 percent of what they were in 1960.

The number of medical school graduates in psychiatry has increased in quantity and in quality.

Now, approximately 11 percent of all medical specialty residencies are in psychiatry, and the percentage of active physicians specializing in psychiatry has increased over the past decade from about 3 percent in 1953 to about 7 percent at the present time, and a high proportion of the new psychiatrists come from the upper 25 percent of their medical school class in terms of scholastic achievement.

This is not to say that there still are not shortages; that shortages are not still a pressing problem. The States by and large are beginning to exert additional efforts of their own, as we knew they would when our program started.

STATE SUPPORT OF LOCAL PROGRAMS

Fifteen States now have Community Health Acts, which allow the State to share with the localities in the development of mental health services. Now, Indiana, Connecticut, California, Minnesota, New Jersey, Vermont, Maine, South Dakota, Wisconsin, Oregon, South Carolina, Utah, Wyoming, and Rhode Island have such services. The

largest, of course, is New York, which provides nearly \$15 million of State money, which matches about \$20.5 million of local funds.

Rhode Island, the most recent State to enact such legislation, has a 50-50 matching program, in which the State puts up 50 cents per capita population in the State.

My own State of Kansas has a somewhat different plan; one which interests me. They have authorized the counties to levy a mill tax on themselves not to exceed one-half mill. This is the same as the mill tax provision for schools; and counties can join with one another in setting up community mental health centers. I like this idea. It promotes, I think, local initiative. We have seen some rather exciting things happen in Kansas as a result of this.

MENTAL HEALTH CENTERS

Mental health centers are developing in a number of places. In Fort Logan, Colo., they have a comprehensive center now, which cared for more than 700 patients during the last year. They provide a wide gamut of services: nighttime hospitalization, day hospital, foster home care, outpatient service, halfway home, and an alcoholic division. San Mateo, Calif., has such a center which is one of the most complete. Kansas City, Mo., has one; 600 patients were cared for in those 70 beds last year, and 1,400 outpatients were treated in the center.

In Illinois, they are developing six community health centers over the State. These are more regional in nature. They will cost about \$8 million apiece. They will provide a full range of services. Two of these will be started this year, one in Chicago's north side and one in Rockford. Other centers are planned in the next year or two for Chicago's south side, Peoria, and Springfield.

Decatur is going to develop one which will have a children's branch in Champaign.

Louisiana has such a one in Baton Rouge.

There are other States: Rhode Island, South Dakota, Wyoming, New York, Massachusetts. There is an interesting development in Delaware. The law has been amended, in Delaware, to permit private psychiatrists and other physicians to send their patients into the three hospitals under the control of the State, and charge these patients, or collect from their health insurance. These arrangements are made with the hospitals, so that the patients can pay for their hospitalization as if they were in a private hospital. It is working very well.

Now, in addition to the progress made in the States, there have been a considerable number of research accomplishments. I know that you have not much time. I would like to mention just three or four of these, because they are particularly interesting.

RESEARCH ON FREE, FATTY ACIDS IN THE BLOOD

Study has been carried forward on the increased free fatty acids in the blood under the influence of emotions. As you know, free fatty acid is the form in which the fat goes from the fat depots of the body to the organs which burn them.

Our investigators used hypnosis on a group of subjects, hypnotizing them, and then suggesting various emotional states. They found

free fatty acid was mobilized particularly under the emotion of anger. Now, this has some interesting implications, because we do know, also, that one of the principal ingredients of a depression is anger.

Mr. FOGARTY. One of what?

Dr. FELIX. One of the principal ingredients is anger. You may not think of this at first, but a depression is usually the result of a—I am talking about what we call depressions developing from the inside of one's own self, not the kind of depression from the loss of a loved one; but it is due to the frustration of an angered impulse.

If you talk to depressives, and if they are not so sick that they can still communicate with you, you will hear them say such things as, "I could kick myself." "I have failed." "I have been a complete flop." "I want to destroy myself."

Mr. FOGARTY. As compared to an outburst of emotional anger?

Dr. FELIX. That is right.

If you get it out, even by fighting, you don't feel depression. One of the groups in which we see depression, not infrequently, are people, let's say, under a boss or under a chief where they cannot express their resentment, but they boil inside, and sooner or later, these people very frequently become quite depressed. They even commit suicide. Once in a while, they may turn the other way and work on the chief, but usually discretion prevents this because they don't gain at all this way. They lose their job and may even go to jail.

Now, the question we want to trace down from here is, Could it be that atherosclerosis should be included among the psychosomatic disorders? If it is true that a number of these emotions, anger, anxiety, fear, increases free fatty acids, could it be that we will find a higher incidence of atherosclerosis in people in whom these emotional states are chronic? And if so, maybe we can get at some of this business, partly by psychiatric means as well as by other means. Drug therapy, and so forth.

DEVELOPMENTS IN PSYCHOPHARMACOLOGY

In the field of psychopharmacology, there are two developments that I would like to mention, Mr. Chairman, and gentlemen. We have found a phenothiazine derivative called Eninthat, which seems to be an injectible form of the compound, and which if injected into the fatty deposits in the body, will be effective for as long as a couple of weeks.

Now, if this is true, this may be a substance we can give, by injection, to uncooperative patients to be effective for a rather prolonged period of time, or we can treat patients at home with this, and they will not have to come back to the clinic every few days for a refill of their drugs. We know they get it. It is being absorbed. It has one hazard of course, and that is that someone else does not repeat the dosage in the period of time the drug is effective.

We have found another phenothiazine derivative, acetophenazine, which is specific for paranoid types in schizophrenia.

Now this is what we have been working toward for a long time: substances which are specific for specific conditions.

One of the interesting studies has been carried out at the Lafayette Clinic in Detroit. Dr. Gottlieb and his group have developed—they

have been working to find some protein factor in the blood of schizophrenics. They have developed a biochemical test, which will determine what they call the lactic acid/pyruvic acid ratio in blood serum. They found if they put chicken cells in schizophrenic blood serum, and in normal blood serum, that is, compare one with the other, that the LP ratio, the amount of lactic acid to the pyruvic acid in the schizophrenic under stress is much higher than under normal conditions.

We were a little skeptical, so we asked some of the group out at Lafayette Clinic to come to the NIMH in our laboratories and to repeat this test blind, which they did on a group of schizophrenics and a group of normals, and they did not know which were which; but they were able to identify the schizophrenic blind in a high percentage of the cases.

This, we think, is a very interesting development.

MENTAL RETARDATION RESEARCH

In the field of mental retardation two or three studies, I think, are important.

It appears now, as a result of some work that has been carried on during the past year by one investigator, on a mental health grant, that thyroid hormone can be administered in extremely large doses to pregnant women, and that the thyroid hormone will successfully pass the placental barrier and thereby prevent the development of cretinism, a type of mental retardation caused by hypothyroidism, in the fetus and in the baby after birth. They found further that a fetus can have hypothyroidism for a period of time; then develop normal thyroid functions, so that at birth, you do not immediately know. The child does not seem to have anything wrong with it. However, certain stigmata will give some evidence of what happened. Umbilical hernia; prolonged cyanosis at birth; high birth weight, over 9 pounds, are three indicators which should cause one to follow up on these cases.

In mongolism, they found that a high proportion of the parents of these children are insensitive to the taste of quinine and other bitter substances. This seems to be related in some way to hyperthyroidism.

So now we have a test that may be able to alert a person to the fact that he or she might have a mongolian child; not necessarily every time, but it can be at least a warning.

Phenylketonuria is the PKU disease. They have now found that such children who are identified within the first 2 or 3 weeks of life, and are put on a phenylalanine free diet, can be taken off this diet at about 4 years of age, and they will develop normally.

One other thing here. We are also developing now more adequate diets for these children, so they don't have such a monotonous diet, and we are developing some laboratory tests, so they can check the phenylpyruvic acid level in the blood, at periodic intervals, just as you check a diabetic.

Mr. FOGARTY. That is what I was going to say. I understand that in Massachusetts all hospitals are cooperating on a statewide evaluation of this blood test, while the child is still in the hospital.

Dr. FELIX. That is correct.

Mr. FOGARTY. I don't know the results, I don't know how long it has been going on. I was just informed of that recently. I think it is the first statewide test in the country.

Dr. FELIX. Let's see. Virginia has developed—has that started yet?

Mr. VAN STADEN. It was started in July 1962.

Dr. FELIX. It was recently started on a statewide basis as a result of a demonstration grant from the NIMH.

We selected Virginia because it is close at hand and we can follow it very closely. There may be one or two other States—not statewide—but there are areas in California.

Dr. TERRY. What is the status of the diaper test?

Dr. FELIX. The diaper test has been improved now, so that they are able to detect PKU disease if it is present, in the first couple of weeks in life, and this is being used. They place some iron—ferric chloride—impregnate a piece of paper with it and place the paper in the diaper during the first 2 weeks of life. If they get the proper color change, they can identify PKU before they show any psychological changes at all.

HEALTH INSURANCE COVERAGE

One other finding, I think, in another area, and then I will be finished with my summary, Mr. Chairman.

I have told you over the last several years, of a grant that we had in operation with Group Health, Inc., a nonprofit health insurance group, in New York. This has been completed; their data have been analyzed; and we think it is of extreme importance.

There were 76,000 people in this study; less than 1½ percent of these people filed claims for psychiatric treatment, either inpatient or outpatient, during the 3½-year period that the experiment was active.

The average cost to carry a case to termination of service was \$186. Some individual cases cost more, of course, and some less.

For most patients, the project was their first experience with the psychiatrist, and because it came through this means, they seemed to be much more willing to accept it than had it been through some other, and the psychiatrists reported that three out of four of the patients they treated under this plan were recovered completely, or so significantly improved, they did not need further intensive treatment before the expiration of their entitlements.

I hope that this information will get about, over the country, because this is a very important aspect of our future plans. It appears as though if health insurance plans will include this they are not going to lose money. More people will be able to avail themselves of psychiatric care, inpatient or outpatient, much earlier. There will be much less drain on the public treasury for patients who have spent everything they have because they started too late, because they were afraid they could not afford it, and there will be an improvement all around.

Mr. FOGARTY. Are you talking about organizations like the Blue Cross?

Dr. FELIX. Yes, sir.

Mr. FOGARTY. What is their policy now?

Dr. FELIX. Well I have some information on that. Commercial insurance companies insure about 56 percent of those with hospital insurance; they usually cover mental illness in their basic policies for groups.

Mr. FOGARTY. I think in Rhode Island we have the highest coverage of any State in the country.

Dr. FELIX. That is true. I was just going to say that. That is correct.

I have just referred to coverage for groups. About a quarter to a half of the policies held by individuals exclude mental illness. I am not an actuary of course, but I still do not see why.

Most commercial companies include coverage for mental conditions on a restrictive basis. As of January 1962, we had the following information regarding 67 Blue Shield plans: 30 percent provide regular coverage of physicians' fees for in-hospital treatment for nervous and mental conditions, 40 percent limit coverage to fewer days than for other illnesses; 5 percent allow benefits only under a very special rider; and the remaining 25 percent exclude mental illness altogether.

Of the 32 Blue Shield plans, offering major medical coverage, 28 have benefit for mental illness care but they are less than the amount for other illnesses.

PROGRESS

Mr. Chairman, I think I am ready now to say that, due to the help and guidance and the encouragement that we have gotten from this committee and from the Congress as a whole for the last 15 years, we are ready to go; and the budget which you have before you is a sound, tight budget, which will allow us to implement all aspects of the enlarged plan—the President's national mental health program—that we can implement under existing legislation.

I could not be more enthusiastic; I have never been more enthusiastic about the prospects of what can be done than I am at this time, nor over the budget which you have before you.

I will be happy to answer any questions you or the members of the committee may have.

Mr. FOGARTY. Thank you, Doctor.

I have been listening to you since you have been appearing before this committee. What was the first year you appeared?

Dr. FELIX. That was the old Mental Hygiene Division before the Mental Health Act passed in 1946 but we began—I began to testify before this committee in 1945.

Mr. FOGARTY. Well, I must correct a statement I made, then.

I have not been listening to you since you first arrived.

Dr. FELIX. Very nearly so.

Mr. FOGARTY. Since the early days of 1947; and you told us a pretty dreary story about the problems of the mentally ill in 1947.

Dr. FELIX. Yes, sir.

Mr. FOGARTY. I think the statement you have just made is one of the outstanding statements of progress that has been made in any of the institutes that I have listened to in 17 years on this committee. I think you deserve a great deal of credit, because you have been heading this Institute since it was established by Congress. Everyone who has anyone in their family that has this particular problem certainly

should gain a great deal of hope for the future from this statement you have presented this morning.

SUMMARY OF BUDGET

The appropriation for 1963, adjusted for comparability is \$143,200,000 and the request for 1964 is \$190,096,000 an increase of \$46,896,000 and 142 positions.

UNFUNDED APPROVED GRANTS

I notice that you have no unobligated balance estimated to lapse at the end of the year. Are you going to have any approved applications for research projects at the end of the year that you will not be able to fund?

Dr. FELIX. Yes, sir. I anticipate we will.

We anticipate that there will be slightly over a million dollars worth of approved, meritorious applications in the research area for which there will not be funds.

FUND TRANSFER AUTHORITY

Mr. FOGARTY. You do not have authority to transfer funds from other institutes, do you?

Dr. SHANNON. Mr. Chairman, we do not have the ability to transfer funds from one appropriation to another. We do have the ability, usually, to make transfers from one activity to another within a given appropriation.

Mr. DORAN. I think they once had a 5-percent transfer authority, and then HEW asked for it and the Labor Department had such authority, but later lost it.

Dr. SHANNON. It was in the appropriation act, but later it was taken out.

Mr. DORAN. The authority was in the general provisions, which provided for not to exceed 5 percent.

Mr. FOGARTY. What if you had that provision today, in the Institutes of Health?

Dr. SHANNON. That would have an impact on our program for the remainder of the year. It would cause quite a difference in the mental health appropriation where there are shortages which could be made up by transfers from other appropriations having surplus funds. We now have a rough idea of the order of magnitude of anticipated balances in the appropriations. These could total as much as \$25 million in accrued balances. I don't believe we can use more than a small part of these balances by making transfers between the activities, as the figures would show. At the same time, in some program areas, there would appear to be deficits that cannot be funded without the authority to make transfers between appropriations. In the aggregate these total about \$17 million. In a program of this size, funded from a series of appropriations and controlled by activity, there is an inevitable need to make adjustments as programs develop in order to utilize funds most effectively. I believe that the Department from time to time has requested transfer authority, in order to make the total appropriation a more effective weapon in the operation.

Mr. FOGARTY. But 5 percent would help considerably?

Dr. SHANNON. If there were authority to transfer up to 5 percent out of each appropriation, I think this would be adequate to cover these eventualities.

AREAS OF FUND SHORTAGES

Mr. FOGARTY. All right. Are there any other parts of your program that could use to advantage more funds than you have for 1963?

Dr. FELIX. Yes, sir.

Mr. FOGARTY. Go right down the list.

Dr. FELIX. Well, there are only three; we could use, in round figures, \$300,000 more in fellowships and about \$5 to \$6 million for training grants.

Mr. FOGARTY. \$6 million more for training?

Dr. FELIX. Yes, sir. They will be approved projects.

HISTORY OF TRAINING PROGRAM

Mr. FOGARTY. I remember when you first testified before the committee—we had outside witnesses, too, like the Menninger brothers and others—and you all said at that time, the big problem was a shortage of personnel. The committee also expressed, from time to time, their thoughts that we ought to be spending more money in the training of psychiatrists, and as a result you have done a pretty good job.

There are other institutes that are not doing a good job at all in training, and I am going to ask the Neurological Institute about this when they come up. I think they are in worse shape than anybody else at the present time, and I cannot understand why we are not spending more money in training in that field.

What were some of the obstacles or some of the problems that you ran across over the years in trying to get a training program up to where it is now. And you say you could use \$6 million more in this field.

Dr. FELIX. As I look back over 15 years, it seems as though every problem in the world was facing me at one time or another. We did not have places where these people could be trained.

Mr. FOGARTY. Do you mean medical schools?

Dr. FELIX. In the medical schools, schools of nursing, social work, they were inadequate insofar as the number of students they could take. Psychology. All of them.

Mr. FOGARTY. What did you do about that?

TRAINING TEACHERS

Dr. FELIX. You will remember, because this was in the days when you were first on the committee, that I insisted that we needed, first, to train teachers. This was our first job. We could not train any more students until we had more teachers.

You may remember I was pushed from time to time: Why are you not getting more people out in the hospitals; out in the clinics? I said, "Give me time. I am not ready yet. I cannot do it yet, until I have the machinery to put them out there."

Gradually, we began to acquire these teachers.

If you look about the country now—while I am reasonably familiar with all the fields, my own specialty, the field of psychiatry—if you look about the country now, you will find that a number of the chairmen of the departments of psychiatry who have been appointed to their chairs in the last decade as well as other persons in leadership roles in psychiatry, were trained on NIMH money—stipends—and in a program which was assisted by the Institute.

I can just go down the list.

Mr. FOGARTY. Well, you can supply some of those examples for the record, at this point.

(The information follows:)

The following is a list of some of the present leaders in psychiatry who received stipends for part or all of their psychiatric training from NIMH funds.

1. Dr. Floyd Cornelison, chairman, Department of Psychiatry, Jefferson Medical College of Pennsylvania.
2. Dr. Albert J. Stunkard, chairman, Department of Psychiatry, University of Pennsylvania School of Medicine.
3. Dr. Seymour Pollack, chairman, Department of Psychiatry, University of Southern California School of Medicine.
4. Dr. Lloyd C. Elam, chairman, Department of Psychiatry, Meharry Medical College, School of Medicine, Tennessee.
5. Dr. Richard A. Steinbach, chairman, Department of Psychiatry, Georgetown University School of Medicine, Washington, D.C.
6. Dr. Melvin Sabshin, chairman, Department of Psychiatry, University of Illinois College of Medicine.
7. Dr. James M. A. Weiss, chairman, Department of Psychiatry, University of Missouri School of Medicine.
8. Dr. Edward T. Auer, chairman, Department of Psychiatry, St. Louis University School of Medicine, Missouri.
9. Dr. Herbert S. Ripley, chairman, Department of Psychiatry, University of Washington School of Medicine, Washington.
10. Dr. John Paton Filley, associate professor and department chairman, School of Public Health, University of North Carolina.
11. Dr. Paul D. MacLean, Chief, Section on Limbic Integration and Behavior, National Institute of Mental Health, Bethesda.
12. Dr. Harold L. McPheeters, commissioner, Kentucky Department of Mental Health, Louisville.
13. Dr. Harold C. Miles, county director of Community Mental Health Services, County of Monroe, Rochester, N.Y.
14. Dr. Russell R. Monroe, professor, School of Medicine, Department of Psychiatry, University of Maryland.
15. Dr. David J. Vail, medical director, Minnesota Department of Public Welfare.
16. Dr. Robert J. Weiss, chairman, Department of Psychiatry, Dartmouth Medical School, New Hampshire.

FACULTY SUPPORT GRANTS

Dr. FELIX. Now, after we began to get these people in the spots, then our next job was to get them on full time, particularly in psychiatry.

Before that, when I was a student, and later, when I was teaching, one engaged in practice and came in and took his class, and then went back out to practice, and this was the accepted custom. We felt, and the whole field of medical education has felt for some time, that what we needed were full-time professors.

So we began to make grants to these schools, which would allow full-time support of faculty. We did this in two ways; we broke the program into two parts. There was the undergraduate

program and the graduate program. We now make grants in the field of psychiatry up to \$25,000, to each medical school in the country.

DIFFERENT PROBLEMS IN PROGRAMS OF OTHER INSTITUTES

Mr. FOGARTY. Prior to that, we were giving grants in heart and cancer. They were giving more help to more medical schools in this area of heart and cancer than the area of mental health at the beginning, when we made up this program.

Dr. FELIX. Yes, but if I can say it, sir, this is not quite fair to heart and cancer. They have a different job than I have. In many ways, my job is easier than theirs. I am training a specific breed of people to take care of mental illnesses, and the mental health program, the way we develop it, the way we have administered the program, the way it is set up in the Public Health Service, is one ball of wax. I have the whole thing, training, research, service and control. But in heart and cancer, you are training surgeons, and internists, and pathologists, and radiologists, and I don't know what all. They do not have a specific kind of a person. There is not a department of cancer or a department of heart, by and large. I suppose there may be some.

Mr. FOGARTY. These funds are given to these schools for the specific purpose of teaching in the area of cancer and in the area of heart.

Dr. SHANNON. Could I interject a comment here that I think is very pertinent to the discussion. I think it may be overlooked and if it is overlooked, the record will be quite distorted.

Mental health, by the nature of the medical care that is delivered, has been accepted in general by the States as a State responsibility. The mental health program, right from its inception, has had a very heavy component of straightforward service in both the training program as well as in the other grants that it has made available. Now, in the area of training in which Dr. Felix is concerned, namely, the production of psychiatrists, rather than the production of general practitioners, he is heavily involved in a major operation that produces medical specialists. In no one of our other institutes is the medical service relationships between the finished professional and his operating base comparable to that in psychiatry. Generally, therefore, we have been unwilling to develop broad programs that involve, primarily, medical care.

Mr. FOGARTY. I think Dr. Endicott said almost the same thing yesterday, did he not?

Dr. TERRY. He did.

Dr. SHANNON. Yes, sir.

Now, in the past appropriation, there was specific comment that caused pretty serious ulcers within the Public Health Service, and that had to do with what type of training would be extended in the field of neurology. The Senate report particularly indicated a need for us to be more aggressive in the training of a variety of neurological personnel for service in the community. This in part, was interpreted to mean provision of trained ancillary medical personnel essential to those programs, therapists, nurses, social workers, etc., as well as the production of neurologists. That is, full certified neurologists, who will have a community service, or inpatient orientation.

Now, the decision has not been made in a positive way to go forward with the straightforward training of neurologists for service. I would point out that neurology is just one example of a critical shortage area; one could point out many other such areas in the training field.

Mr. FOGARTY. Worse than neurology?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. We had testimony here, some years ago, that there were some States that did not have a qualified neurologist, and in a four or five-State area in the Southwest, there was only one.

Dr. SHANNON. That is true.

Mr. FOGARTY. That is a few years ago; but I did not think any other field was in as bad a condition as that.

Dr. SHANNON. Yes. In certain areas of radiology and pathology, there is an equal shortage of essential personnel to the extent that medical facilities are not operational to full capacity. These are service operations and NIH training programs have not addressed themselves to the satisfaction of this service need. I might say that if this were done our training funds would require a tremendous expansion as compared to their present levels.

Mr. FOGARTY. Some neurologists would not agree with that statement; that I know. I am not talking about people in the Government now but outside of the Government.

I thought Dr. Endicott did a pretty good job yesterday, when I raised the question with him, whether or not they should be training more people in the field of cancer, and he said it was entirely different than mental health.

Go ahead now, Doctor.

You said the first obstacle is the lack of teachers.

Dr. FELIX. Then as we began to develop these, and we made grants to the institutions, so that they would be sure and have a spot, and be paid for it, we began to push the schools to absorb into their own budgets those people who are on what is known as tenure positions. Usually associate professors and professors. We kept insisting that Federal money was soft money, and they should not consider it as anything else.

To a significant degree, this has occurred.

MOTIVATING STUDENTS TO ENTER PUBLIC SERVICE

There is one other thing we began to be asked: "Will these people trained on your stipends be required to deliver any kind or amount of service?" My answer to this was:

If we put this kind of a stipulation in, we are going to downgrade the quality of people, and I want all of those people to be well trained; but I have another way of doing it, plus the fact I want to be very sure that the Federal Government * * *

and you have heard me say this almost every year I have been up here, Mr. Chairman:

I want to be very sure that the Federal Government does not get its hand into dictating educational policies, educational procedures.

This, I think, would be a most dangerous thing. I can think of few things so threatening to our democracy as to have the Federal Government call the tune on what is taught and how it is taught; but to assist the schools is another thing altogether.

So we made funds available for these professors of psychiatry; professors of psychology; and other groups, to meet by regions. We made grants to them. They organized themselves: The Association of Southern Professors of Psychiatry; the Western Professors of Psychiatry, I think it is called. The Northeast Professors of Psychiatry are presently being organized as a group.

They would meet and discuss mutual problems.

Now this had, I think, the proper effect, in the good old American way of doing it, because somebody would have a new idea and he would report it, and someone else would get real nervous, because he did not have this thing going on in his place; so they asked questions. And obviously, the reporting school was moving ahead of the other school. There would be a lot of questions, and soul searching, and the first thing you know, they would either be developing it on their own money or coming to see if they could get some supporting funds from us, where they could not include it in their own budget, and develop this particular area of teaching.

So we did one other thing.

We pointed out to these professors of psychiatry and psychology and so forth, that these students were being educated on Federal funds. We thought it was incumbent upon them to do everything possible to instill into these students a real motivation for public service in some form: teaching, research, or working in public situations.

We pointed out for instance, that in some schools, my school, for instance, this was so successful, even back more than 30 years ago, when I was a resident psychiatrist, that almost every alumnus of my school, the University of Colorado, who went into psychiatry, has gone into some form of public service.

This was accepted with real enthusiasm by these professors. The results are that less than 4 percent of those people trained on our stipends are not engaged in some form of public service, to the extent of a significant portion of their time. They may be in private practice part time, but it is less than 50 percent, and the great bulk of this group are devoting their time in some form of public service, in clinics, in hospitals, in teaching, research—something of this nature.

I don't know what others think, but I must say now, as I look back, I am more pleased with our decision to move this way than I was at the time I started. I was nervous that this would not work. It has worked. So now, we see that these programs are becoming attractive. People want to go into them. The number of the top level of the graduating classes in medicine who want to go into psychiatry and into these programs, has increased.

The fate of these people has been, by and large, public service. This has been true in psychology; it has been true in nursing; it has been true in social work.

Now, at the same time of course, the cost of living has gone up. It has been necessary for salaries to go up. This has been taken care of primarily by the States and localities. As you know, the \$6.75 million in State grant funds, our grants to States money, is substan-

tially overmatched this year by about \$120 million of State and local money.

This has increased to a significant degree because of increased program but it is also increased, in part, because of increases in salary, which have been necessary in order to hire these people, and as the ball is rolling now, I am confident when I say that I believe that the number of professionals in these fields, working in the field in 1960, can be doubled by 1970. This would mean about 86,000 to 87,000 of them by 1970, if we keep rolling as we are.

Mr. FOGARTY. Does that complete your statement?

Dr. FELIX. Yes, sir.

EFFECT OF TRAINING PROGRAM ON QUACKERY

Mr. FOGARTY. When we have this increase in personnel in the field of psychiatry, what degree has this affected quackery in the field of psychiatry?

Dr. FELIX. Well, I think that it influenced a decrease. It is my feeling that people still feel that their first choice for help is the traditional family doctor. As long as they can get help from the family doctor, usually, they will not look elsewhere. There are always some deviants, who will, but by and large, they will not.

In order then, to make it possible for the family doctors better to care for their patients, we have, as you know, instituted through your help, the committee's help, the general practitioner's training program, for which there is \$9 million requested this year, or an increase of \$2 million.

This has made it possible for a large number of physicians—even-
tually, I hope it will be all—better to treat their patients. When they run into a complication which is beyond their capacity as a practitioner, they refer it to a psychiatrist, a specialist, who picks up the case at this point, because now families and individuals can find this kind of help. I do not hear the same amount of complaints about quacks in this field as I did, well, 15 years ago.

Mr. FOGARTY. Well, I still hear of people going to some of these quacks, and they keep going and going and going and not getting anywhere.

TRAINING PROGRAMS FOR GENERAL PRACTITIONERS

Now, you mentioned the training of general practitioners. I was going to ask that question anyway, but now that you mentioned it, would you describe the program and tell us whether you have had enough money to take care of all those who sought this additional training.

Dr. FELIX. There are two parts to this, Mr. Chairman. As you know, we make funds available to appropriate training agencies, to universities, to medical societies, in many cases, such as the Academy of General Practice; the American Psychiatric Association; the State Medical Societies, and so forth, to put on training programs for the physicians with whom they are concerned, to give them more information about the psychiatric aspect of their patients.

The other part of the program allows for people in the practice of medicine, other than psychiatry, who have been in for 4 years or

more, to apply for a full residency in psychiatry and become psychiatrists.

Now, of course, the great bulk of people go into the former. That is, they remain in their own field.

NUMBER PARTICIPATING

Let's take fiscal year 1964, this particular year. It is estimated there will be about 3,200 physicians who will take these post-graduate courses, and return to their practice better equipped to practice. There will be a total of about 600 who will have left their practice to go into psychiatry and will be in a full time residency.

Now, because these people are established in practice, because, if they are not established, and successful, they don't get by the selection boards in these training centers, they have incurred financial obligations which makes it impossible for them to take this psychiatric training program—I am talking about the full time residency training—at the levels provided for the young intern.

So there are provisions for stipends of a larger amount for these people, depending upon how many children they have and what kind of obligations they have.

This program started in the fiscal year 1959. I was anxious to see it start. I hoped it would go over.

Mr. FOGARTY. Is that a table you have?

Dr. FELIX. Yes, sir.

Mr. FOGARTY. Put that in the record.

(The table follows:)

History of the general practitioner program 1959-64

	Number	Amount
1959:		
Residency training.....	94	\$1,000,000
Postgraduate education.....	1,500	300,000
Total.....		1,300,000
1960:		
Residency training.....	185	1,900,000
Postgraduate education.....	1,700	400,000
Total.....		2,300,000
1961:		
Residency training.....	304	3,100,000
Postgraduate education.....	2,200	700,000
Total.....		3,800,000
1962:		
Residency training.....	413	4,500,000
Postgraduate education.....	2,800	900,000
Total.....		5,400,000
1963 (estimated):		
Residency training.....	473	6,000,000
Postgraduate education.....	3,000	1,000,000
Total.....		7,000,000
1964 (estimated):		
Residency training.....	609	7,800,000
Postgraduate education.....	3,200	1,200,000
Total.....		9,000,000

PROBABLE FUTURE EXPANSION

Dr. FELIX. I have been amazed, and I did not think I could be amazed any more, at how this program has caught on. I believe that if we continue, with the consent of the administration I will in future years ask for more money for this. I think we can cover every doctor in the country—almost every doctor in the country and the day we do, we are going to see a lot of patients who never have to go to a psychiatrist and this is the answer to it, and the doctors want it.

Mr. FOGARTY. How much do you think we would have to appropriate to do that? Over how long a period of years?

Dr. FELIX. I am not prepared right now to give you a definitive figure. I can go back and do some calculating.

Mr. FOGARTY. All right.

(The material follows:)

There are at present approximately 57,000 physicians in full-time private practice as general practitioners. At the 1964 level of support for postgraduate education in the NIMH general practitioner program, about 3,200 will enroll in these postgraduate courses around the country. About 14,400 will have participated in such courses between 1959 and the end of the courses supported out of 1964 funds.

It is not known how many of the 57,000 have already had some psychiatric orientation. However, if the greater proportion of these physicians are to receive such orientation it can be accomplished in 5 additional years beyond 1964 at an annual rate of 4,000 per year and an annual cost of \$1,500,000.

While this is being accomplished, however, a new batch of graduates will be coming out of the medical schools, who could also be making good use of such postgraduate education. In view of the much more extensive inclusion of psychiatric education in today's medical school curriculum, these new doctors will not be in as serious need of postgraduate education in psychiatry as some of the older physicians of today who took their medical education 10 and 20 years ago. Nonetheless, this program should not be abruptly discontinued, even after an additional 5 years of operation. A reevaluation at that time will better determine the needs beyond that point.

Dr. FELIX. Now, this I have not discussed with either the National Institutes of Health, the Public Health Service, or the Department in definitive terms, so it should be understood I am completely on my own.

Mr. FOGARTY. When this program was started, it was not at the suggestion of the Public Health Service or NIH. It was a suggestion that came from outside.

Dr. FELIX. Yes, sir. But in all due justice to the Service and the Department, they did not drag their feet.

Mr. FOGARTY. No, they did not. You were not really sold on it though, and neither was I. I did not think it was going to catch on like it has.

Dr. FELIX. I did not think it was going to go like this. It just spread like wildfire.

Mr. FOGARTY. How much could you use in 1963?

Dr. FELIX. I think we have about the right amount.

Mr. FOGARTY. \$7 million?

Dr. FELIX. We could have used another \$600,000 in 1963.

Mr. FOGARTY. And 1964 is about right?

Dr. FELIX. About the right amount, I believe.

Mr. FOGARTY. You will not have any applications that you will not be able to fund in 1964?

Dr. FELIX. If we do, they will be of a low enough priority that they ought to think them through again, anyway. I do not want this money to go out except on a good sound basis.

PSYCHIATRIC TRAINING FOR CLERGYMEN

Mr. FOGARTY. You also give grants to three religious schools: Jewish, Protestant, and Catholic. What are these schools again?

Dr. FELIX. The three schools are Yeshiva Rabbinical Seminary in New York, Loyola Jesuit Seminary in Chicago, and Harvard Divinity School in Cambridge, Mass. The latter is the Protestant seminary.

Mr. FOGARTY. Just briefly describe this particular program.

Dr. FELIX. We have been concerned for a number of years over the fact that large numbers of people, quite appropriately, go to their clergymen with their troubles—many kinds, including emotional troubles. A survey made some years ago revealed that there was nearly—not too far from 50 percent of the people who have troubles go to their clergy.

The clergy would come to us from time to time and tell us that they just were not prepared to deal with many of the things and they had no place to turn. They had no psychiatrist and the family doctors felt they were not able to deal with many of these problems.

So we got the idea of putting on a pilot project, and this should be underlined, that this is a pilot project. It is not an overall underwriting of this sort of thing in religious schools—in theological seminaries. It is a project to learn what should be included in the curriculum of the various seminaries which would be consonant with their faith and dogma and also with good psychological-psychiatric teaching and at the same time would be most effective to the congregations, the parishioners.

These were negotiated grants and we did it this way because we had requests before from this or that denomination. We declined to make a grant until we had a multifaitth set of applications. So that all three of the major faiths were working simultaneously. These three groups consult with one another, exchange information, and out of this have already come several publications, books, and articles about what should be in the curriculum in the various faiths.

One very interesting report came from the project at Loyola. Father Devlin, who is now dead, made a study of what, in the psychological area, were the pastoral duties of a priest. He describes the priest's role in mental health. It is a most magnificent presentation.

The Yeshiva project has resulted in a series of reports on the impact of religion on emotions and in this case the rabbi dealt with these problems of the parishioners. Harvard put out a syllabus and has put out one book, reporting on the results of their teaching and the followup of the first seminarians, on what has happened to them and how they have gotten along.

Now, I know a little bit about this from another point of view. I have considerable interest in my own church in the training of clergy and I have been able to follow some of the seminarians and to have consulted with them when they are assigned out to parishes.

I am amazed at how much more sophisticated these men are now than they were a few years ago, as they begin to get this information.

Now, this is different. What we are talking about here is different than what was formerly called chaplaincy training.

Mr. FOGARTY. What do you mean by "sophisticated," the way you used it?

Dr. FELIX. They have at their fingertips a better understanding of what is going on with their parishioners and what they can do about it, consistent with their faith, with their teachings, and also when to let go and call for help.

Dr. TERRY. I think that is one of the important things—not only what they can do, but what they cannot do.

Dr. FELIX. I do not think the clergy or lawyers or any group should be psychiatrists, junior grade, any more than the psychiatrist should be a clergyman, junior grade; or a lawyer, junior grade.

A person has to know when to let go and call for help. What is happening, as a result of this, these clergymen from these three seminaries, have gone into parishes and congregations and have lined up two or three doctors they can call on for help.

Mr. FOGARTY. Do you think it has been a worthwhile pilot program?

Dr. FELIX. Excellent. I do not regret one cent that was spent on this.

ABSORPTION OF MANDATORY COSTS

Mr. FOGARTY. All right. How much in Pay Act and similar mandatory costs are you being required to absorb in 1963?

Mr. VAN STADEN. \$255,000 was the cost of the pay raise absorbed in the 1964 estimate; the total for mandatory items is \$505,000.

Mr. FOGARTY. This is 1963?

Mr. KELLY. \$407,000 was the mandatory cost occasioned by the Pay Act and related acts that were absorbed by mental health activities in 1963.

INSERVICE TRAINING PROGRAMS

Mr. FOGARTY. This committee made a few recommendations in our report last year. We recommended, first, that you expand and extend training programs for service and research personnel. You explained that in your statement.

Dr. FELIX. In part.

Mr. FOGARTY. Do you want to add to it?

Dr. FELIX. Yes, I would. I welcome the opportunity to say a word about an item in this budget which to me is extremely important. In addition to the other extensions, you will find contained in the written justifications of the training grants, an item of \$3 million-plus labeled for inservice training. This is what the committee was asking, I am sure, and we are very enthusiastic about the prospect. These funds, if appropriated, will be granted as the first of a 3-year buildup. We wish to make a grant up to but not more than \$25,000 to one-third of the State hospitals for the mentally ill and for the mentally retarded, doing all we can to assure that there is at least one in every State for the purpose of assisting in the development of inservice training programs in these institutions.

This is part of our total long-range push in which we hope to promote and assist in the upgrading of the care and treatment of the mentally ill, thereby reducing the need for prolonged hospitalization. This is part of the grand strategy designed to reduce the size of the

State hospitals and place the responsibility for patient care, treatment, and rehabilitation on their home communities.

This program will require about \$3 million this first year. These inservice training programs will permit subprofessional people particularly to be much better trained—people like attendants, so they will be able to care for the patients more appropriately. We will move to the second third in the second year, and the third in the third year. We would expect these funds to be spent at the hospitals, not some center, but at the hospitals, in order that the programs will touch every employee in the hospital.

Now, back of this I have another idea which meets with favor, as far as many commissioners are concerned. I would like to see a career system for these subprofessional people developed in the States, which will cut down the high turnover in personnel. In some States the personnel turnover in these categories is 100 to 125 percent a year.

Mr. LAIRD. Are you providing that on a hundred percent basis, this inservice training?

Dr. FELIX. I would hope not.

Mr. LAIRD. What kind of matching is it?

Mr. KELLY. There is no provision for matching.

Mr. LAIRD. Then how do you know this is not 100 percent?

Dr. FELIX. I do not think they can do the full job for \$25,000. I think they are going to have to have money to do it. This is training of subprofessional personnel, in-service, on the job. The very fact, Mr. Laird, that they are taking these people off the wards and allowing them an extra amount of training time is money. They are not caring for patients at this time. This is good, hard money in itself. I want to see a program developed where all personnel in this attendant category will come in as a sort of apprentice and they will have 3 or 4 months during which they spend most of their time in the in-service training. Then they will take a qualifying examination, and it will be up or out. If they qualify, they will go up to the journeyman level. Once they reach that level, they may begin to take inservice training, which will qualify them for the supervisor or master's level, which will come along at a later period. As they are able to qualify for this, they will be—as we used to say back home in Kansas on the railroad—they would be on the extra board. They would be eligible for appointment to responsibilities as vacancies occur. This would occur if there is a proper escalation of salaries for these positions. This would give us a class of trained people with some reason to stick around and continue to work, which would give continuity in these hospitals and improve tremendously the quality of the care given these patients.

STATE MENTAL HEALTH PROGRAMS

Mr. FOGARTY. Are they doing anything similar to this in Kansas?

Dr. FELIX. They are at the Topeka State Hospital.

Mr. FOGARTY. Is there any State that has a better record in mental health than Kansas?

Dr. FELIX. I do not like to be put on the spot because I love all the States equally. Kansas is my home State.

Mr. FOGARTY. I am thinking of the Menninger Institute out in Topeka. I have been told year after year that that has helped tremendously.

Dr. FELIX. It has.

Mr. FOGARTY. And it is holding trained psychiatrists there in the State.

Dr. FELIX. On the other hand, California is doing magnificently under Dr. Blain. They have cut the number of patients in hospitals down. They are going to be able, they feel, to reduce their hospital population 50 percent, despite the rising population. New York is doing an excellent job under Dr. Hoch and his colleagues. Connecticut is among the leaders with their decentralized regional hospitals. Illinois, while not doing as well as they want—and they would be the first to say so—in the hospital part, with these new regional centers which are to be built, is going to have one of the best programs in the country. Yes, Kansas would rank in the first half dozen. There is no denying it, and I would say it without any Kansan's self-consciousness at all. One of the reasons, other than the hospitals, is the new community mental health act which they have passed and which allows the counties to develop their own programs. It is most exciting what can happen under this provision. In my home State there is Finney County which at first blush would be thought to be one of the most unlikely spots in the whole State to see a program like this develop. It is the second county up from the Oklahoma line and second in from the Colorado line, down in the southwest corner of the State.

Mr. FOGARTY. Do you think that is one of the best in the State?

Dr. FELIX. It is a program out on the broad prairies, with a psychiatrist and psychologist serving. There are now three counties being served and the number of admissions to the hospital has dropped very significantly since this has developed.

TREATMENT OF ALCOHOLICS

Mr. FOGARTY. I recently heard a State doctor say one of our worst problems today in the State hospitals is the chronic alcoholic. They are given space in many of these State institutions and that is about all.

Dr. FELIX. If you ask me, I do not believe an alcoholic belongs in a State hospital. Never have. I did not think so when I worked in them, and I do not think so now.

Mr. FOGARTY. Nothing much is being done for them?

Dr. FELIX. By and large little constructive is done beyond drying them out.

Mr. MICHEL. What percentage of patients in mental hospitals are there due to alcoholism?

Dr. FELIX. Mr. Michel, I will have to get that for the record. I am not sure.

(The material follows:)

The percentage of patients resident at the end of 1960 in public mental hospitals due to alcoholism is 3.4 percent.

PRINCE GEORGES COUNTY PROJECT

Dr. FELIX. We started a project at Prince Georges County General Hospital over here in the neighboring county to the District, in which

they would provide hospital beds under contract and personnel for the treatment of acute alcoholics in the general hospitals.

Mr. FOGARTY. What is the difference between a chronic alcoholic and an acute alcoholic?

Dr. FELIX. An acute alcoholic, a person in an acute alcoholic state, is one who is drunk as opposed to a person who may be nipping away but he is not really drunk.

Dr. FELIX. They have been treating patients in acute alcoholic intoxication there now successfully for about 2 years. This has led to an interesting development.

Now, they do not need as many beds as were originally contracted for, so they are using the rest of the beds for the treatment of acute psychotic patients who are brought in. It is now pretty well demonstrated through this project and some others, that we can treat alcoholics in the general hospitals and also treat psychotics. This has had an important bearing on treatment programs and on hospital policies.

EFFECT OF INTENSIVE CARE BY TRAINED PERSONNEL

A study was made recently which tended to demonstrate that those alcoholics who are brought in who are really down-and-out drunks, who get intensive care from skilled people, are many time more likely to return for followup care after they have been dried out, detoxified, than a person who has just been hospitalized and sent home.

By and large, with the alcoholic, if we can prevent him from taking the first drink, as you know, we are safe; because they tend to develop a sensitivity to alcohol, so that with one drink they must have more. It is almost a biological hunger that they have which I described here several times before for this committee. It becomes essential then to keep them away from that first drink.

Now, as is true with addicts and barbiturate users and others, the alcohol becomes a means they use to try to cushion themselves against the slings and arrows of outrageous fortune. So they will turn to this almost instinctively.

The thing is if they establish some contact such as with a clinic, with a physician, with someone of this nature, they will turn to him before they begin to drink. Within the last 2 weeks I had an individual whom I had been trying to help for some time, who called me up. It was after midnight. I was in bed. He wanted to know if he could see me immediately. He said, "If I can't see you in the next hour, it won't do any good." He came over to the house—this man had been having some emotional difficulty. Had I not seen him at that time, I am sure he would have been drunk by morning, probably in the station house by evening, and 8 months of good hard work would have gone down the drain.

I listened to him; I heard his story, and then I took a rather direct approach, pointed out to him that he was a drunk, would always be a drunk, but could avoid drinking. He had to remember that he was never safe and that he was going to be in danger of ruin at any time.

After about an hour he went home, called me up later in the day. He weathered this particular crisis and is still dry. This is the kind of contact that we need for these people.

ALCOHOLICS ANONYMOUS

This is why such groups as Alcoholics Anonymous—

Mr. FOGARTY. They do a pretty good job, do they not?

Dr. FELIX. They certainly do. I have said many times that Alcoholics Anonymous have done things for patients of mine when I had been unable to.

Mr. FOGARTY. They have some real dedicated people in this group that go out all hours of the night like this example you have given.

Dr. FELIX. That is right.

Mr. FOGARTY. They will go right to the house, will they not? I know many that have.

Dr. FELIX. They go to the house, and they will sit with the person and will point out, "Where you are now, I was a year ago, 5 years ago, or whatever it is—I know exactly what you are going through. I have been there. I could be there tomorrow if I took a sip."

Mr. FOGARTY. But still the problem is growing, is it not, in this country?

Dr. FELIX. Yes, it is.

Mr. FOGARTY. Chronic alcoholism is on the increase?

Dr. FELIX. It is on the increase. We do not know the answer to this yet, and it is a difficult area in which to stimulate research.

FUNDS ALLOCATED TO STUDY OF ALCOHOLISM

Mr. FOGARTY. How much money are we spending on this? Do you have a table breaking it down?

Dr. FELIX. Yes, sir. From 1960 to 1964.

Mr. FOGARTY. Put that in the record.

(The material follows:)

5-year expenditures for alcoholism

[In thousands]

	1960		1961		1962		1963		1964	
	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount
Grants:										
Research-----	41	\$1,069	44	\$1,263	57	\$2,003	46	\$2,320	70	\$3,000
(Title V)-----	(6)	(156)	(8)	(252)	(15)	(562)	(14)	(395)	(20)	(500)
Fellowships-----										
Training-----			2	58	2	76	3	100	4	130
Total, grants-----	41	1,069	46	1,321	59	2,079	51	2,424	78	3,140
Total, direct opera- tions-----		70		70		170		322		250
Total, Insti- tute-----	41	1,139	46	1,391	59	2,249	51	2,746	78	3,390

Mr. FOGARTY. I remember this committee gave you an initial amount of \$750,000, 4, 5, or 6 years ago?

Dr. FELIX. \$3,390,000 this year.

Mr. FOGARTY. I have some more questions that I have to ask, but it is getting a little late so we will pass the questioning around and I will ask these other questions later.

Mr. Denton?

Mr. DENTON. Doctor, I want to congratulate you on the statement you made. Like Mr. Fogarty, I think it is one of the best I have heard, and I think you can be very proud of the work that you are doing.

DEVELOPMENT OF TRANQUILIZING DRUGS

You spoke about the amount of money that has been saved because of the way that we treat mental illness now. Is that not due very largely to one or two things: One, the grants that have been made by your Institute which have developed the tranquilizing drugs, which have had such a desirable effect in treating people who are mentally ill; and two, because of the training of psychiatrists which has been brought about very largely by the training and fellowship program of your Institute?

Dr. FELIX. On the second you are entirely correct, and on the first you are partially correct; for it should be remembered that private industry, the pharmaceutical houses took the major brunt both in risk money and in effort in developing the tranquilizing drugs.

We have been active for a number of years in trying to assess these drugs, trying to find out which are good and which are not so good, and trying to provide information to people who are researching in the field. But I would not want the record to show that the drug houses did not play a very major role in the development of these drugs.

Mr. DENTON. Rauwolfia was discovered under a grant that your Institute made, was it not? Did not Dr. Klein do the work on that?

Dr. FELIX. Yes, sir. But, remember, rauwolfia had been used for about a thousand years in India and was used in this country primarily by the heart people as a means of reducing high blood pressure. It was noticed that people not only had reduced blood pressure but they seemed to be much more relaxed and calm, and so then Dr. Klein got an idea and wondered if there were not a possibility it would work in mental patients. This is where it moved over into the psychiatric field.

Mr. DENTON. That was done with a grant from NIH, was it not?

Dr. FELIX. I believe his original work was done other than by a grant from us. We have supported him in projects since, however.

TRAINING PERSONNEL

Mr. DENTON. Now, you spoke about people being trained by NIH. Last week three people came into my office from my district who were welfare workers. Their particular work was with disturbed children. I understand they are doing very good work, but they all stated they had been trained under grants from NIH, which I was very pleased to hear.

But I still think there is a great deal to be done in training psychiatrists. I mentioned this before, but one doctor told me in a mental hospital that he had 600 patients. He said, "If I could treat these patients, I could get a great many of them out of here." He said, "About all I can do is give a lick and a promise."

Now, it seems to me that it would be much more economical to train psychiatrists to get those people out of the hospital than keep them there. I cannot think of any other disease a man might have

where he would not have a doctor to treat him. If he had heart trouble, cancer, or even a common cold, he would get medical attention; but here are 600 people in a hospital that do not have adequate attention.

Dr. FELIX. This becomes very real. If a person needs help for himself or a member of his family, and he is faced with a situation like this, I have had people ask me, "Why can't we have it better," and our answer has been, "We are moving as rapidly as we can, but I know too well what your problem is." This hurts. This hurts way down deep.

DIFFICULTY IN STAFFING STATE HOSPITALS

Mr. DENTON. You spoke about this but it is difficult to get psychiatrists in State- or Government-owned mental hospitals because the remuneration is much more outside.

Dr. FELIX. This is true, although even many of those who are outside are working part time in clinics, working in general hospitals part time, hospitalizing their patients in general hospitals.

Well, the whole problem is very simple, if you have to move into a situation where you were responsible for this number of patients at the kind of salaries that you are paid, or if you were paid any kind of salary. I would not work in the average State hospital for \$50,000 a year, and I could use \$50,000 a year. I just could not stand the situation professionally.

Mr. DENTON. What do you think we can do? We have to have doctors at the State hospitals.

Dr. FELIX. We are now moving in a number of States. Your State is beginning to do it under Dr. Ginsburg. Other States are doing it. They are what we call regionalizing these hospitals, so that you take a hospital like Indianapolis or any one of the others in the State, and you break it down, say, into four subhospitals, each serving a certain number of counties. As soon as you do this, you have to staff up differently. You cannot have the doctor running all over the place. He has to be responsible for this group of patients over here. This increases the ratio or makes the ratio more favorable of doctor to patient, nurse to patient, social worker to patient, and so forth.

Now the doctor has something to get his teeth into, where he can actually know his patients and work with them.

Mr. DENTON. I went on this committee when this Institute was a very new agency—I think in 1951—and I remember the great difficulty at that time that you had in getting trained personnel. I think you have reached a point where you are getting some results, now, from that program that we had instituted.

Dr. FELIX. That is correct.

RESULTS OF RESEARCH PROJECT ON GOATS

Mr. DENTON. I remember one thing that happened early that year as a result of an experiment with goats. Somebody wrote up an article that Oscar Ewing was taking the public money to find out why goats baa. I remember the explanation you gave was very good and as a result of that experiment we were able to tell during the Korean war when men had battle fatigue and probably saved a good

many lives by that experiment, by being able to take men out of the frontlines before that condition got too bad.

Dr. FELIX. That is right. The knowledge gained through that experiment conducted at Cornell they were able to apply in Korea to battle fatigue and were able to predict that a man had about reached the breaking point, pull him out of the lines, and put him in a rest camp until he could recoup. And as a result, they cut down significantly the combat fatigue cases, the psychiatric types. I do not care how rough, tough, strong, and mentally sound a man is, if you leave him in the front lines long enough and let enough of his buddies suffer casualties, he is going to crack if you do not bring him back and give him a rest.

We found this out certainly in the Italian campaign during World War II, in which there were outfits in some cases in which the men were 60 or so days continuously on the line. Before they got through there was not a man, if he had not been wounded otherwise, who was not incapacitated psychologically.

ALCOHOLISM

Mr. DENTON. About intoxication. I understood there are some people who should never take a drink because if they take one drink, they cannot stop until they cannot drink any more. Is that what the case is?

Dr. FELIX. That is right. As a matter of fact, if the person came to me and asked me what would be the most important single warning sign, I would say that when you drink because you like the effects of drinking, rather than drink because you are with the boys, you are in danger. There have been some studies on this. When you drink because you want the effect, you are taking it like medicine, you are in trouble.

Mr. FOGARTY. Mr. Lesinski?

Mr. LESINSKI. Dr. Felix, you have made some statements here which I am glad to hear, and which I shall get into in a bit.

First of all, you were distracted by another question. You did not complete the statement. The differences in alcoholics, differences in human beings and the way they can absorb liquor. You were distracted at that point.

Dr. FELIX. Well, I sort of made it a little bit later. Some studies have been completed now which seem to indicate that there are really two types of drinkers.

They can be heavy drinkers or light drinkers. One group drinks only with the crowd and he can go any length of time and face any kind of situation where he does not take a drink if he is by himself or to help master the situation. There is another group who apparently drink because they want the effect—they either—it may be that they want to be able to be more relaxed in a group or they want to be more effective in dealing with someone, they want to be less embarrassed if they are in a strange situation, they don't want to be so blue or whatever it might be.

The former group by and large do not become alcoholics. The latter group—if their drinking begins to increase significantly, and if

one other thing happens, they are showing signs of trouble. This other phenomenon is very interesting. As their drinking increases they reach a point rather suddenly where their capacity has gone way up. All of a sudden they have a hollow leg. Because something happens in the body at a certain point whereby the body is sensitized to alcohol and at this point there is a period they have not gone completely over the edge in which the body throws out an enormous amount of enzyme which metabolizes alcohol and a little bit of alcohol stimulate the production of the enzyme.

Now, he takes a large amount of whisky or liquor and he metabolizes it.

He goes a little further and get to the point where his intake increases above the capacity of the enzyme in the blood to metabolize it.

Every time he takes a drink he stimulates the cells to put out some. So he can go without drinking for let us say, 2 weeks—without drinking for a year if you will. He takes one drink and this triggers off a reaction in the body not like, but you can compare it to, a reaction like hives or other allergic responses.

A small amount of alcohol, maybe an ounce or two or less will trigger an enormous production of this enzyme.

Now the body has this need for alcohol because they have got the stuff there to metabolize it and no alcohol to metabolize. This creates a sort of physiological hunger. So when a person finds the intake increasing he is drinking because of the effect of the drink and he finds that his capacity goes up, he is in trouble if he does not stop right there.

Mr. LESINSKI. It is like a person smoking a cigarette. If he smokes cigarettes heavily for a long time and cut it out for a while, the first cigarette you take knocks you for a loop.

Dr. FELIX. That is right. That is interesting because I smoked my last cigarette a year ago yesterday noon. I still have got the habit because it still smells awfully good. I know if I smoked a cigarette now, I would be quite dizzy so I do not like to be dizzy and I convinced myself that this is no way to be so I am able to live from day to day and not smoke.

Mr. LESINSKI. I thought you were hitting at the differences of individuals as to the ability to or not to drink as some people can take one drink and they are done.

Others can take three or four and it does not bother them.

Dr. FELIX. That is something else. There are people who have what you might call pathological alcoholism. That is, one drink and it is like a poison. Literally, a smell of the cork will knock them over. A small amount of alcohol will render them intoxicated in the sense of being poisoned, toxified. This is another group.

One other thing that happens one must look out for, another warning sign of the alcoholic, is when he blacks out—does not pass out, blacks out.

This can happen occasionally and it usually happens more frequently as time goes on. This is when they go out on their feet and nobody knows they are out. The next day they do not know where they have been or what they have done.

SAFEGUARDS AGAINST GOVERNMENT INTERVENTION IN HIGHER
EDUCATION

Mr. LESINSKI. You pointed out—you mentioned the fact that you would not like to see governmental control of the hospitals and universities and so forth. And I commend you for that statement. On the other hand, if there is not individuals like yourself in Government, they might take over control of universities.

Dr. FELIX. Mr. Lesinski, I do not think so. It will take a minute to explain. I am just one person out of a kind. There are a number like me. I believe my attitude is typical of the Public Health Service. There would have to be a complete turnover of top personnel in the Public Health Service before this could ever happen.

Mr. LESINSKI. I appreciate that.

Dr. FELIX. I do not think we are rare in Government. I do know my chief, Dr. Shannon, and my big chief, Dr. Terry, and others, and how they feel. They would not tolerate this.

Mr. LAIRD. It sounds like some sort of Indian tribe you have over there.

Dr. FELIX. We are a good tribe too, I am telling you.

On the other hand, suppose this did happen. We have to come back every year and account to you folks and you folks come from back home and you are not going to let this happen.

I cannot imagine sitting in front of five men in this committee or your opposite numbers in the Senate and hearing any, or at least a majority of them, insist that this sort of thing happened or even countenance it if it were happening.

Mr. LESINSKI. It has happened in democracies in Europe at one time or another. There is a parallel.

Dr. FELIX. This is true. But only if you relax your vigilance, if I relax my vigilance. If you would push me, I would resist you, because I try to always be alert and sensitized to this danger.

I would resist you to the point, sir, that if you insisted I would quit. I will not do it. On the other hand, if I insisted, I should be fired.

Mr. LESINSKI. One of the most difficult forms of government to live under is a democracy that we have for that very reason. You have to watch that all the time.

Dr. FELIX. It is not the most economical way and not the most rapid way. But it is the best way, I think.

ADVANTAGES OF TREATMENT NEAR HOME

Mr. LESINSKI. You mentioned the many drugs you have developed and the use of them for psychiatric treatment and also the need of additional hospitalization.

It would seem to me as these findings are a means of treating the patients—you can treat them more rapidly and you would need less hospitals.

Dr. FELIX. Eventually we will. As we are able to develop facilities in the communities, and this is where a person ought to be treated.

Did you ever stop to think how ridiculous it is—a person has difficulty getting along in his community. This is the place he has to

live. This is the place he has to go back to. You pick up and take him 300 miles away where he is around a lot of people just like himself except for the staff.

And then you expect him to come back and fit in? If you keep him home, allow him to have inpatient treatment for the minimum time necessary, he has a much better chance of fitting in the community.

Mr. LESINSKI. I have a case. I would like to have an answer to this. There was a well-respected individual in my neighborhood and married and he was caught—anyhow, playing with boys. I do not know whether there was any final action.

There was some inducement. He was sent to prison by the judge and he was able to get the minimum—it is up to 15 years in Michigan for homosexuality. He did get the minimum, 1 to 5, and he could have been released after 9 months.

Well, I interceded. I thought the man was well respected and this was his first offense, to my knowledge. Now, and in my rationalization of the case, if he was let go to come back to his community and the people in the neighborhood knew about it, he would tend more not to be caught and not to fall into the same paths but if he was kept in the institution he would fall into the same thing you would not want him to be.

Dr. FELIX. I would say you are right with one addition. There would not be any good resulting from sending him back home unless there were some conditions. He may have the impulse at the wrong time when there is nobody to stop him and there may be trouble.

There ought to be some place he can turn in the community for treatment because the man is sick.

This was the basic reason why you recommended as you did rather than recommending that the law take its course. This was not a malicious offender, this was a sick person. If he is a sick person, he needs treatment and I agree with you, his treatment should be given at home rather than way off some place.

TRANSFER OF FUNDS BETWEEN ACTIVITIES

Mr. LESINSKI. Have you the authority to—in your listing of your grants for research and fellowship—have you authority to transfer funds from one to the other?

Dr. FELIX. You mean research to training and so forth?

Mr. LESINSKI. And so forth.

Dr. FELIX. Yes, but I am going to ask one of the administrative people to tell you about it.

Mr. KELLY. The authority exists to do that.

The Surgeon General exercises the authority. We have established a relationship with this committee that you do not have to place limitations on how much is available for research grants and fellowships because we follow the activity structure we give you and if there is an occasion for a significant modification in our program that would make a significant change between the amounts for those activities, then we would communicate with the committee and inform you of the change and these changes are only made by the Surgeon General.

The authority is not delegated below him.

Mr. LESINSKI. Now, off the record.

(Discussion off the record.)

PROPER LEVEL OF FINANCING

Mr. LESINSKI. One more question I had regarding taxation. The interest stirred by the administration in cutting taxes has been my position since 1951. We have a matter of responsibility to the people of our district and again, I repeat, everything you have done, have said, I have to commend you for, but if we are to do what the administration is requesting, do you not think we should be within reason in approaching financing?

Dr. FELIX. Mr. Lesinski, I can speak as a citizen who pays taxes, who votes in the community for his local and State and Federal officials.

I can speak as a professional who sees these needs and who sees these sick people and who has to go out among them and cannot eat his meal when he comes back because of what he sees knowing it does not have to be.

I could speak from either of these points of view. But let me put it this way: This Congress has spent since 1948 about \$675 million in the field of mental health through the National Institute of Mental Health.

This is no small amount of money. You have been so successful in your investment that today we can move forward and I can tell you that with your backing and your support we can cut the size of mental hospitals in half in a decade or two.

Now, the amount of money at the outside that it will take to do this is a fraction of the amount of money it will take to do—I will not mention anything specifically because I think all things in the Government need money.

Mr. LAIRD. You are not sure of that, that all these Government programs really need the money.

Dr. FELIX. As a public servant I would assume so unless shown otherwise.

You are going to get—you have gotten us to the place where we are ready to go. It is either go or step back.

We have got people ready. We have got the techniques ready.

We have got communities ready. Organizations such as the American Medical Association, the conference of State Governors and so forth are ready to go.

It is like D-Day. If you do not go now the weather may change or things will change and you cannot do it.

I am by no means the person to judge whether or not we should do so much or twice so much or half as much.

I would feel that this would be wrong for me to take this point of view. I should be the professional, I think, who comes to you and says, here is what we can do, here is what we are ready to do.

You know the total picture. How much is needed for this, for that, for the other, and what priorities this should have.

And certainly I always have—and I do now tell you again. I will abide by your decision. I will do the best I can. But I am delighted that I have the endorsement of the kinds of organizations and people that I do have and the backing of the administration in saying, "let us go."

Mr. LESINSKI. The point is, all of you have testified before us so far and have mentioned the glaring successes you have had in your various

fields and the results have been astounding and I can appreciate the effort you have put into it.

If the effort, the past effort you have done with the finances supplied by the committee are successful, why, therefore, should the program be enlarged as you suggest here?

Dr. FELIX. You could have asked me that 5 years ago, why should it not have been enlarged and I would say what I say now.

If it is not we will not achieve the next step. We are ready to move now. We have been hung up for 15 years tooling up. The chairman asked one of the early questions about this whole training field.

We could not have moved from homeplate halfway to first when we started. Now we are ready to score.

TRANSFER OF FUNDS BETWEEN ACTIVITIES

Mr. LESINSKI. That is why I asked the question before. Can you transfer funds from grants to training? I got the answer there and if you can cut down some duplication in your grants, for instance, cancer has over 2,000 grants—I do not know how many grants you have here—I understand the need of grants.

But your request is for training the proper personnel to utilize this information; am I not right?

Dr. FELIX. Yes, sir. I want the record to be straight. I believe that Mr. Kelly may have misunderstood your original question.

Do you think so?

I thought you asked me whether we could transfer in the National Institute of Mental Health under the appropriation item "Mental health activities" between research and training.

Mr. Kelly gave you the answer to that. If you mean transfer between research-cancer and training-mental, the answer is "No."

Mr. LESINSKI. No. You are right. I appreciate that. But in your own mental activities, you can.

Dr. FELIX. The Surgeon General has the authority, and I believe whether it is law or custom or regulation he always consults with the committee.

Mr. LESINSKI. After the committee makes its decision and it does not quite meet the original request, you may sit down with your Director and decide what is the best.

Dr. FELIX. Yes, sir.

Mr. LESINSKI. I appreciate that.

Dr. TERRY. It should be emphasized that it has been very rare where we have felt that the circumstances were such that we have shifted between categories and have come back to the committee to request or get the committee to assent.

We felt this is the pattern in which we should operate and we should depart from the appropriation pattern only under the most unusual circumstances.

I do not think we average coming back once a year to the committee to request any change.

PROPER LEVEL OF FINANCING

Mr. KELLY. Mr. Lesinski, you made a statement that I do not think is quite correct. You said the problem was training and we had

acquired the knowledge. We are a long way from having everything acquired—from having acquired information on how to treat all types of mental illness. We have made sufficient progress but we have not in any sense completed the research that is needed.

Dr. FELIX. Thank you. I missed that.

Mr. LESINSKI. I will accept that. You are at a plateau now which is way higher than ever before in the past.

The point that I am driving at is, by simply giving you more money does not mean you will be able to expedite the findings.

Dr. FELIX. Not by simply giving us more money but by giving us money in areas where we need to move forward still and where we are ready to move forward, I would submit you are promoting the program more rapidly than otherwise would be the case.

There are significant increases in this budget for just this purpose. I feel very strongly that we need these in all the places where they are in the budget to move this program forward.

We need more than this in the future before we get through. But our goal is such that I believe the money will be well spent and returned to you in terms of people back home and reduced expenditures at a later date.

If we just rest on our laurels now, we will not have enough people trained, we will not have enough knowledge to do the kind of job we know is over the horizon.

I am not sure whether you were here on this or not, but I mentioned a very important piece of research in your home State, the Lafayette Clinic in Detroit. Dr. Gottlieb is doing some research of certain types of substances in the blood of schizophrenics. There are two or three research groups like this. We have not yet found the whole story. We are able now with what we know already in terms of drug treatment and better management and the care of patients to see something in the neighborhood of 65 percent of the schizophrenics admitted to hospitals returned home within a year.

A significant portion of these within a matter of months. We can do better than this. I would submit that with proper facilities and people to do it, there is only a small hard core of patients even at this time in our present state of knowledge who need to stay in these mental hospitals and eventually we may not need to have any of them there.

We are not there yet. You cannot leave me now. You must stick with me for a while longer. If you do, we will get there.

Mr. LESINSKI. No more questions, Mr. Chairman.

Mr. FOGARTY. In other words, you could not very well suggest that some of these funds that you have for research grants be shifted over to training because it would disrupt the entire program, wouldn't it?

Dr. FELIX. That is correct.

Mr. FOGARTY. That you have envisioned for 1964?

Dr. FELIX. Yes.

Mr. FOGARTY. If we had done this 4 or 5 years ago, we would not be in as good a position as we are today.

Dr. FELIX. That is correct, and remember in this fiscal year I will have unpaid approved applications.

PROJECT GRANTS TO MENTAL INSTITUTIONS

Mr. LAIRD. Dr. Felix, let us turn to page 159 of your justifications.

You are setting up a new program of making up to a hundred thousand dollar grant to one-third of the mental institutions during the first year, "being certain, however, that at least one institution for mentally ill and one institution for mentally retarded in each State receives funds in the first year."

This is a new program entirely and it looks on the surface like you are just passing out money.

How did this program get started?

Dr. FELIX. Can I take a minute to give you the back up on it and I will try to answer your question.

Mr. LAIRD. You are just going to go to every State. You say at least one institution in every State. So regardless of what might be going on in the State you are going to make a grant to them?

Dr. FELIX. No, sir, that is not correct.

Mr. LAIRD. It says here in your justifications—

* * * being certain, however, that at least one institution for the mentally ill and one institution for mentally retarded in each State receives funds the first year.

Then you go on to say it is—

for the development and prosecution of long-term (5 to 10 years) demonstrations in improved methods of patient care and treatment to hospitals and in the administration of such institutions. The States would be encouraged to submit applications for the first year under this program."

Dr. FELIX. Provided they can qualify.

Mr. LAIRD. It does not say that.

Dr. FELIX. I will say it now for the record, then, because I mean this, too.

We have felt for a long time that in order to see what we are talking about come to pass; namely, placing the responsibility for each patient back in the community, one thing had to happen and that was to improve the care in mental hospitals, so patients will go out faster and go back home.

Mr. LAIRD. That is fine and obviously desirable.

ELIGIBILITY AND MATCHING REQUIREMENTS

Are you going to require the States to match this program or are you just going to pass out the money?

Dr. FELIX. What I was getting up to is this: If this money is appropriated, we will notify the authority responsible for the State hospitals for the mentally ill and mentally retarded in each State that he may select those institutions he wishes to have considered the first year to submit applications with a description of what they propose to do.

We will empanel a committee of individuals expert in the care and treatment of patients in mental hospitals, and hospitals for the mentally retarded to review these applications.

Mr. LAIRD. How is it going to be financed?

Are you going to require any financing by the State legislature?

Dr. FELIX. Not in this. This is a 10-year program—12 years counting the 2 years to taper off at the end. This is a 10-year program up to, but not necessarily at a hundred thousand dollars per year for each State hospital.

Mr. LAIRD. Even though the State does not show any interest?

Dr. FELIX. If the State does not—

Mr. LAIRD. From the standpoint of the elected representatives in that State.

Dr. FELIX. If there is such they do not get it. Or if they have gotten it, they do not necessarily continue.

Mr. LAIRD. What is the matching then?

Dr. FELIX. There is no matching. There does not have to be.

Mr. LAIRD. It is a 100-percent grant.

Dr. FELIX. Just like our present title V grants. It is under section 303 of the act, the authority—we would use the same authority.

Mr. LAIRD. I would like to see these State legislatures show some interest in this before making funds available.

Dr. FELIX. Can I have a minute to try to tell you what is proposed to be done?

If we can get these operating—up to a hundred thousand dollars is a small fraction of any State hospital budget. They run from \$3 to \$6 million a year apiece. This is not subsidizing anything. It will allow them to take 10 or 12 beds someplace in the institution and develop a model program.

Now, the idea of this is, that if they develop such a program, then they can demonstrate as the years go by to their legislature and to their budget people in the executive branch of the State what can be done, thereby initiating this same kind of program or similar ones throughout the entire hospital or hospital system.

They are not going to get this money shoveled out. These applications must be approved by the National Advisory Mental Health Council.

If they are disapproved they do not get it. If they do not get it they just do not get it.

Mr. LAIRD. I think they should be required to show some financial interest themselves, even though it is no more than 25 percent.

Dr. FELIX. Mr. Laird, if you do, you are not going to get this off of the ground nearly as rapidly or as effectively.

SIZE OF PROGRAM

Mr. LAIRD. Dr. Felix, you are talking about a program that could run up to a hundred million dollars. You are talking about a \$5 million program the first year, aren't you?

Dr. FELIX. I am talking about a \$12 million program that will go to a maximum of \$36 million in the third year.

Mr. LAIRD. If you just made it \$100,000 per institution, it would be \$36 million. You are asking for \$12 million for 1964?

Dr. FELIX. You see, we are taking—we are hoping to take one-third of the hospitals the first year.

Mr. LAIRD. If you start making this kind of grant there is no limitation on it. There is no matching and no incentive for the States making a financial contribution to this program. It seems to me that this program could run up to a hundred million dollars.

Dr. FELIX. It cannot run above \$36 million annual maximum. This is what I am defending here and I am on the record here to tell you it is part of the legislative history of this program, that the grants will be up to, not exceeding a hundred thousand dollars a year for 10 years to each hospital for the mentally ill and mentally retarded.

Mr. LAIRD. Why should not the States put in something in this kind of a program?

Dr. FELIX. I am sure they will.

Mr. LAIRD. Why not require them to?

Dr. FELIX. Because if you do, there are States that cannot do it. They cannot do it.

Mr. LAIRD. What States cannot do it?

I would like the names of those States.

Dr. FELIX. All right, I would prefer not to mention it on the record here.

Mr. KELLY. I would think, Mr. Laird, it would be a very difficult program to establish matching in because you are going to be spending money in a State institution which already is spending a significant amount of State funds and it would be very hard.

Mr. LAIRD. States will take this money for nothing, I do not disagree with that. I am sure they will put in their applications but it just does not seem to me that you are going to get the best kind of participation if you do not have to go before the legislatures in those particular States and at least get some minimum interest expressed in this program.

Mr. KELLY. What Dr. Felix was expressing was a philosophical concept and what I am expressing is an administrative management problem associated with it. We have reviewed the statistics in the investment in mental hospitals when we were working on the St. Elizabeths budget.

For the last 10 years the States have put more money in the operation of their mental hospitals than they did in the preceding year.

So even if you say additional money must be used for matching purposes I think you would be hard pressed to identify whether that money was going to be invested additionally or was not; and it would seem to me that you might be better off to establish a partnership relationship in trying to utilize these funds for the purpose of accomplishing their intended results rather than to debate the technicalities as to whether or not they are being matched.

Mr. LAIRD. Here is a whole new program laid out in this justification for the first time. I would like to have this justification on page 159 put in the record at this point if I could, Mr. Chairman.

Mr. FOGARTY. Yes, sir.

Mr. LAIRD. From the second paragraph on down and I would like to put in the record at this point a 5-year table, (fiscal years 1960 through 1964) setting forth each Public Health Service grant to

States program, and showing the amounts granted or allocated under each program.

Here we are embarking upon another grant to States program, of which we already have a great many, and there is no State financial participation required. I think we have to look this program over very carefully.

(The documents referred to follow:)

PREPARED JUSTIFICATION MATERIAL

Page 159 of justifications:

Based on the conviction that the large mental hospital as it presently exists is anachronistic and cannot serve the mentally ill in optimal fashion, many professionals would question the wisdom of the recommendations of the Joint Commission to appropriate large sums of money to support programs of the large public hospitals which would in effect perpetuate them.

In view of these observations, it is believed that the most appropriate support which can be given to the State mental hospitals at the present time is the encouragement of demonstrations of the most modern methods of treatment, care, and upgrading of the staff through appropriate programs of training. The great need is to demonstrate in each State mental hospital the role of adequately trained personnel in mobilizing the available resources to move patients out of hospitals at the earliest date consistent with good psychiatric practice. Although the problems of the mental hospital are not easy to solve, evidence is clear that they are by no means insoluble, and with energy and vision, significant improvements can be effected.

The public mental institution is only one element, albeit an important one, in the spectrum of services available to the mentally ill in the community. The more flexible and dynamic the hospital program, the more easily and fully can it coordinate its services with the community program before, during, and after a patient's hospital stay. In order to assist the State to upgrade quality of care in public mental hospitals and institutions for the mentally retarded the Institute proposes to initiate the following program through the mechanisms of the mental health project grant.

A. Provide grants of up to \$100,000 to one-third of these institutions during the first year, being certain, however, that at least one institution for the mentally ill and one institution for the mentally retarded in each State receives funds the first year.

B. In each of the succeeding 2 years, cover an additional one-third of these institutions within the program.

C. In utilizing these funds for hospital improvement projects different criteria would be applied to applications in this category from those currently applied to applications for participation in this program. Immediately on activation of this program, actions would be taken to:

1. Inform each State that there will be initiated over the next 3 years a program providing an allotment of funds up to \$100,000 per year for each State institution for the mentally ill and institution for the mentally retarded for the development and prosecution of long-term (5 to 10 years) demonstrations in improved methods of patient care and treatment to hospitals and in the administration of such institutions. The States would be encouraged to submit applications for the first year under this program.

2. Establish a special committee of experts well acquainted with hospital programs and problems who would review applications prior to submission to the National Advisory Mental Health Council.

3. Consult with the States as they formulate projects for the remaining two-thirds of their institutions, one-half of which would be submitted for grant support in each of the succeeding 2 years.

An increase of \$12 million is requested for this purpose, \$8 million of which will be used to improve the quality of care in public mental hospitals and \$4 million of which will be used to improve the quality of care in public institutions for the mentally retarded.

Public Health Service—Grants to States

OBLIGATIONS

[In thousands]

Appropriation title (current) and program	1960	1961	1962	Estimated, 1963	Estimated, 1964
Chronic diseases and health of the aged:					
Cancer control programs.....	\$2, 190	\$3, 314	\$3, 389	\$3, 500	\$4, 000
Heart disease control programs.....	2, 905	3, 300	4, 598	7, 000	7, 000
Other chronic disease control programs.....	0	0	4, 859	13, 000	13, 000
Cancer projects.....	1, 347	1, 695	3, 013	4, 750	5, 000
Neurological and sensory disease projects.....	0	0	892	2, 600	3, 630
Other chronic disease projects.....	0	0	2, 294	6, 000	7, 000
Communicable disease activities: Community immunization.....	0	0	0	12, 100	10, 205
Community health practice and research:					
General health.....	14, 985	16, 755	14, 920	15, 000	15, 000
Migrant health services.....	0	0	0	1, 500	2, 500
Control of tuberculosis:					
Formula.....	3, 993	3, 982	3, 499	3, 250	2, 500
Projects.....	0	0	496	1, 250	2, 006
Control of venereal diseases: Projects.....	2, 372	2, 379	2, 575	4, 335	5, 895
Air pollution: Survey and demonstration.....	0	0	13	0	0
Radiological health: State program development.....	0	0	0	1, 500	2, 000
Water supply and water pollution control:					
Control programs.....	2, 901	2, 892	4, 593	5, 000	5, 000
Demonstrations.....	0	0	300	500	625
Hospitals and medical care: Hawaii (leprosy).....	1, 000	1, 200	1, 200	1, 200	1, 200
Mental health activities: Control programs.....	4, 911	5, 942	6, 622	10, 950	10, 950
Construction, mental health facilities, Alaska.....	6, 500	0	0	0	0
Total.....	43, 104	41, 459	53, 263	93, 435	97, 511

ALLOCATIONS ²

[In thousands]

Hospital construction activities.....	\$185, 000	\$185, 000	\$209, 728	\$220, 000	\$170, 000
Grants for waste treatment works construction.....	46, 816	46, 101	80, 000	90, 000	100, 000
Total.....	231, 816	231, 101	289, 728	310, 000	270, 000

¹ This program included in supplemental appropriation estimate that has been submitted to Congress.² Allocations are made to States; awards are made to individual projects, within these allocations.

Dr. FELIX. I would like to say one thing. If the States put in \$5 per patient per day, this much they put in and we put the grant on top of it. They are not riding free.

Dr. TERRY. The important thing is to look upon this as a project grant and not simply a formula grant that will go to the States. This makes a great difference.

Mr. LAIRD. I do not know why you have to make one to each of the 50 States then.

Dr. TERRY. We will not, unless they qualify.

Mr. LAIRD. That is not what the justification says.

Dr. TERRY. I think Dr. Felix made it clear.

Mr. FOGARTY. We will recess until 1:30.

AFTERNOON SESSION

NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

Mr. FOGARTY. The committee will come to order.

Another recommendation we made last year was for increased efforts toward establishing a national clearinghouse for mental health information.

What have you done about that?

Dr. FELIX. We have continued to develop that clearinghouse, Mr. Chairman. We have had the so-called feasibility studies carried on during the present year. We know now how to go about collecting the data we need. The clearinghouse will really have several purposes. It will be a storehouse of information both quantitative and qualitative—that is, both the amounts and numbers, and about kinds, and what is better than others.

Second, there will be a referral center for any authorized people in the country, including the various branches of Government, from qualified State officials or for research investigators. The clearinghouse will analyze and evaluate information with the aim of bringing together discrete bits of information which might otherwise be missed.

We plan, as we begin to gather our data, to submit from time to time careful studies of special problems, such as where do we stand today in schizophrenia; what is presently known and what is presently being done in retardation; in any one of the many fields, in delinquency or other areas.

We are very sure of one thing, now, from these studies. That this information is going to be rather voluminous, therefore it probably will have to be stored and retrieved electronically by machine. We are prepared now to move into the next stage and let contracts for the collection of these data. We have let, or are in the process of letting, two or three contracts at the present time. One contract, I believe, has been let now with the Pan-American Health Organization, which is, as you know, the Western Hemisphere regional office of the World Health Organization, to give us information from all of the Americas on what is going on from both the standpoint of programs, discoveries, legislation, and so forth.

We are in the process of letting another contract—it has not been let yet—with the World Federation for Mental Health in Geneva, for the purpose of gathering similar data about Western Europe. We do not know yet how successful we will be with regard to gathering data from Eastern Europe or from behind the Iron Curtain. We are negotiating now to set up similar resources for Asia.

The principal amount of information of course, will come from this country, from the States. We have an agreement now with the various State mental health authorities and with the universities to supply us with information as rapidly as it comes out. We have transferred into this unit already the information service of the Psychopharmacological Service Center, which is a nucleus of stored information.

JUVENILE DELINQUENCY

Mr. FOGARTY. We also recommended that you give additional attention to the problems of juvenile delinquency, drug addiction, and alcoholism and schizophrenia.

We covered the alcohol problem pretty thoroughly this morning; did we not?

Dr. FELIX. Yes, sir. I think so.

In juvenile delinquency, Mr. Chairman, this fiscal year of 1963, it is estimated that our investment in this field will be something over \$7 million.

We anticipate we will have active about 118 grants of various kinds, research and training in this area.

Our projection for 1964 is reflected in the budget before you. This program will be at the level of something over \$8 million and about 140 grants.

Now there have been several important developments in this field. First, our activities have been along several different lines. Development and assistance and demonstration projects. I will come back to that because there is a large one there.

We have assisted in the training of personnel and the support of research, both basic research, basic to the problem, and techniques of managing it.

DEVELOPMENT OF METHODS OF EVALUATING PROGRAMS

One of the troubles in this field is people set up demonstrations, and there is no really good way that cannot be open to a lot of criticism as to how effective it has been or whether the results would not have happened anyway or not; so we are developing evaluation methods for assessing research.

We are working with the States on surveying their own problems and a number of other areas of this kind.

DEMONSTRATIONS

I want to move rather quickly if I can to the demonstrations. There is about \$4½ million worth of demonstrations this year. The principal one is our portion of the support of the program known as mobilization for youth in New York City.

There are several organizations working together. The President's Committee on Juvenile Delinquency; Ford Foundation; the city of New York; and the National Institute of Mental Health.

In fiscal year 1962, we made a grant of \$1½ million. In 1963, that has gone up to \$1.8 million and our projection for the next year is slightly over \$1.9 million. That is our share. The total project is considerably larger than this. It is over \$4 million.

That has been described in times past, and unless you wish, I will not go into it more deeply.

MOBILIZATION FOR YOUTH

Mr. FOGARTY. Just briefly, tell us about Mobilization for Youth. I know what it is, but just to have it on the record.

Dr. FELIX. The real prime mover and guiding light of Mobilization for Youth is a very brilliant and dedicated man named Mr. McCarthy, in New York, who is extremely knowledgeable in this field of the underprivileged and the delinquent youth and has worked with them as a dedicated person for many years.

He developed the idea, a number of years ago, of taking a discrete area, of a city, and since he knew New York, and was down in the lower East Side, in what they called the Lower East Side Neighborhood Association area, taking a number of blocks of this particular area, and developing a demonstration here, saturating and developing

this area with all of the helping agencies and facilities which have been claimed or have been demonstrated, either one or both, to be deterrent to youth crime, to concentrate them here and to see what will happen.

The Institute of Mental Health originally made a grant for a planning period, for him really to organize his thinking; to have time and freedom from other concerns; to lay out a long-term plan and then to submit an application, which he did, which was reviewed by our council, by the Ford Foundation; by the President's Committee on Juvenile Delinquency and by the city fathers of the city of New York.

This plan is now in operation, and they are bringing into this area skilled people from a whole variety of agencies and activities, who work with youth and will observe the changes that occur in terms of delinquent acts, not only in arrests, but delinquent acts which do not result in arrests; school dropouts, and a whole variety of indexes, which are used to measure the youth maladjustment in delinquents.

Now, I think it should be very plainly stated that no one claims that this is the final answer. If it were, we would set the project up differently.

Mr. FOGARTY. This was a 5-year project, was it not?

Dr. FELIX. That is right, sir, and it may well be, at the end of 5 years, Mr. McCarthy and his associates will say, "Our original idea was wrong. We should have done something different."

"Now, we have to try this," or he may say, "We were 50 percent right or 75 percent right. We need to modify it in this regard."

I think it is important that this be done, and we have a continuing and very deep interest in this project.

DRUG ADDICTION

Mr. FOGARTY. Tell us about your activities in drug addiction.

Dr. FELIX. In drug addiction, our program in 1964 is at the level of about \$21½ million. We have about 49 projects in this area.

Mr. FOGARTY. Do you have any good ones?

Dr. FELIX. Yes, sir. I think we do.

Mr. FOGARTY. What are they?

Dr. FELIX. You remember, I am sure, the project which was carried on with the various agencies in New York City; the police department, the narcotic group, the various helping agencies in which they followed up a series of discharged patients from Lexington, Ky., hospital.

Several things came of this, and to me, the most important thing was not a new finding but something that we thought we knew, and we found was true, and that is, that these various agencies, who before had not touched addicts, on the basis that they were a lot of trouble, or they would cause trouble, could work with them, and constructively work with them, and work with each other.

The patients that were followed were patients who had been through the program at Lexington. They had been patients there; they had been treated there; and were released. The residents of New York were released to the New York area. The demonstration unit was a

unit financed entirely out of the mental health funds, and was really an extension of our intramural program.

Another finding of this study, which I had many years ago suspected, when I was on the staff at Lexington, and that was that something happened to addicts when they got to be somewhere in their early thirties, and they were not quite the same kind of person after that.

Well, what they found in this study in New York was that addicts when they get up in the thirties, are not so likely to relapse to drugs, as they are before that. I don't know why. This is an empirical finding. It is just what we see; and we don't know why yet, but addicts are less liable to return to drugs and are more likely to be abstinent longer after 30 than before. This is a finding which I think must be followed up further, and I think should be capitalized on, because if this is true, rehabilitative efforts in this 30-year-and-above group should be much more rewarding than in other groups.

Additional kinds of treatment, and even institutional procedures, should be established for the younger group of addicts.

I believe those are the principal findings of that New York study. There have been a number of States who have modified their laws in the last year; that is interesting. The Supreme Court of the State of California—

SPECIAL REPORT ON DRUG ADDICTION

Mr. FOGARTY. We will put your special report in the record.

Dr. FELIX. All right, sir.

(The report referred to follows:)

INTRODUCTION

National Institute of Mental Health programs in drug addiction range from studies of the biochemical effects of narcotic drugs to assistance given local and State agencies to deal more effectively with the problem at the local level. Work is carried on through technical assistance projects, mental health projects and research grants, and through research in the Institute's own laboratories and facilities.

Drug addiction apparently is a consequence of physical, psychological, social, and other factors which press on the individual at a critical point in his life. Progress is being made in understanding how addiction develops, but more information is needed. Specifically, more knowledge is needed about the life history of addicts, the impact of social and environmental factors upon them, the effectiveness of different therapeutic approaches and methods, and the basic mechanism of drug action.

In terms of treatment and rehabilitation, it has become increasingly evident that addiction must be viewed as a chronic, often intermittent, illness, requiring followup rehabilitation within the community after hospital care.

NIMH-SUPPORTED DEMONSTRATIONS

The New York Demonstration Center, established in 1957 through Institute support, was terminated in early 1962. A report of its operations is being prepared for publication. The Center was a demonstration project in which selected patients discharged from the U.S. Public Health Service Hospital in Lexington, Ky., were referred to appropriate community agencies. In addition, staff from the Center conducted longitudinal studies of relapse and adjustment to the community among discharges.

Originally, it was felt that the Center's most difficult problem would be obtaining the cooperation of local New York City agencies, but this did not prove to be the case. Almost all agencies approached agreed to extend services to

referred patients; in some cases, this required a revision of policy which opened the door of these agencies to such patients for the first time. Activities of the Center also helped disprove some generally accepted ideas about addicts; for example, staff members found that the patients and their families had strong interdependent relationships and that, frequently, the families needed as much help as the addicts.

Experience gained in this project will be utilized in a second 5-year demonstration, set up through a contract with the Medical & Health Research Association of New York City, Inc. This second demonstration project will be conducted in the New York City Department of Health's Washington Heights District with the collaboration of the health department and the New York Community Mental Health Board. Social workers, public health nurses, and other staff members from the Washington Heights Rehabilitation Center will provide treatment and aftercare for addicts, assess community needs for addiction control, and investigate effective rehabilitative techniques.

The Washington Heights Center, which will handle both self-referrals and cases referred by cooperating courts, will emphasize maintaining contact with drug users and developing methods to encourage abstinence. A full-time social scientist will be responsible for evaluation of the project, while consultation will be provided by representatives of several scientific disciplines.

STATE AND LOCAL PROGRAMS

The following are examples of activity in the field of drug addiction on both the State and local levels.

California revised its administrative code in sections dealing with facilities for treatment and rehabilitation of addicts. This State is also developing the former Corona Naval Hospital near Los Angeles into a California Rehabilitation Center which will provide treatment facilities for 2,300 patients.

Section 11721 of the California Health and Safety Code, which declared it a criminal offense to be addicted to narcotics, was declared unconstitutional by the Supreme Court on June 26, 1962, on the grounds that it constituted a cruel and unusual punishment in violation of the eighth amendment. The majority opinion in the 6-to-2 decision stated that while California could make hospitalization or treatment mandatory for addicts, it could not make addiction itself a criminal offense.

Colorado has initiated, under the State department of parole, a new followup procedure for paroled addicts, which involves the use of thin-layer chromatography for faster and more effective detection of narcotics in the urine.

Philadelphia has an Institute for Alcoholism and Narcotic Addiction as part of its Division of Behavioral Problems, Pennsylvania Department of Health. The institute collaborates with Philadelphia General Hospital and the Philadelphia Department of Health. Also in this State, the board of parole has established an experimental narcotic unit in its Philadelphia district office. Staffed by a clinical psychologist, an assistant district supervisor, and four experienced parole agents, the unit accumulates data to help establish actuarial tables and provide a basis for new concepts in the treatment and supervision of addicts and other compulsive offenders.

In New York, the Metcalf-Volker law went into effect January 1, 1963, making this State the first legally to recognize narcotic addiction as an illness. The law provides a basis for voluntary admission of addicts to special facilities and permits judges to authorize medical treatment rather than imprisonment where feasible. Under Metcalf-Volker, a drug addiction unit headed by a special assistant to the commissioner will be established in the New York State Department of Mental Hygiene. In addition, a council on drug addiction, consisting of the heads of certain State public agencies as well as designated citizens, has been established to advise on policy and help develop long-range addiction programs.

Hospital facilities for addicts in New York State include a 55-bed unit at Manhattan State Hospital, a basic research center, plus an 80-bed unit at Central Islip State Hospital and a 20-bed unit at Utica State Hospital. The hospitals provide immediate treatment and long-range rehabilitation for addicts admitted either voluntarily or as court referrals.

Since early 1961, New York City has had a narcotics coordinator. This official, an assistant commissioner of the city's department of health, has expanded his staff and is planning extensive activities in such areas as research, education, and consultation.

INTRAMURAL RESEARCH

The NIMH Addiction Research Center located at the U.S. Public Health Service Hospital in Lexington, conducts research in the pharmacological, neurophysiological, biochemical, psychological, and socioeconomic aspects of drug addiction.

Tests of new analgesic drugs

Addiction properties of new analgesic (pain relieving) drugs are tested in a program closely coordinated with the Committee on Drug Addiction and Narcotics of the National Research Council. The program has four major aims:

(1) To provide information on the degree of addictiveness of new drugs, and thereby to determine whether they should be subjected to national or international legal controls;

(2) To develop pain relieving, cough suppressing, and constipative drugs with reduced addictiveness;

(3) To provide information on therapeutic and toxic properties of these drugs prior to their introduction into clinical practice; and

(4) To discover the basic mechanisms of tolerance, habituation, physical dependence, and other aspects of addiction.

The goal of discovering a potent, pain-relieving drug with little or no addictiveness appears closer than ever before. Some years ago, the Addiction Research Center demonstrated that nalorphine, the first narcotic antagonist, was not addicting, yet relieved pain in man. Unfortunately, nalorphine was found to be an impractical analgesic because it causes serious mental side effects. Current research focuses on the search for other narcotic antagonists without unfavorable side effects; the most promising appear to be those of the benzomorphan group, developed in the Laboratory of Analgesics, National Institute of Arthritis and Metabolic Diseases.

Two of these compounds are of particular interest at the moment. The first, although a weak antagonist, is approximately one-half as potent as morphine for pain relief in humans, is not addictive, according to Addiction Research Center tests, and seems to produce few, if any, unfavorable side effects. The second is a potent antagonist and a very potent painkiller, since 0.5 milligram or less is equivalent to 10 milligrams of morphine. It does not seem to be addictive and while it does induce some mental abnormalities, they are milder and less frequent than those produced by nalorphine. Additional clinical testing, particularly with patients requiring continuous pain relief over long periods of time, is needed.

Psychotomimetic drugs

The psychotomimetic drugs, including cocaine, marihuana, and mescaline (the active principle in the peyote cactus used by American Indians), induce temporary psychotic states and hence are important both in terms of public health and as keys to understanding of such psychoses as schizophrenia. Recent research concentrates on tolerance and cross tolerance among these drugs with a view toward separating them into biologically related groups, in the hope that such a classification will provide important clues to their action. However, patients made tolerant to cholinergic blocking drugs are not cross tolerant to LSD; rather, the reaction to LSD is enhanced. Therefore, it seems clear that the cholinergic blockers constitute a group biologically distinct from the LSD group. Also, the LSD psychosis is not due to inhibition of cholinesterase or to increased formation or release of acetylcholine.

Since 6-Hydroxydimethyltryptamine is not a psychotomimetic drug in man in doses of 2 milligrams per kilogram, it cannot be the active form of dimethyltryptamine, as has been suggested, since the latter induces a striking psychotic state in doses of 1 milligram per kilogram. There is no, or only a very low degree of, cross tolerance between LSD and dimethyltryptamine.

PSYCHOLOGICAL STUDIES

In this area, clinical studies have four major emphases: (1) the psychopathology of narcotic addiction, (2) study of the subjective effects of central nervous system drugs and the relation of those effects to personality characteristics, (3) determination of the variables influencing social deviance, and (4) studies of the effects of drugs in cycles of addiction on psychophysical measures.

As an example of one type of research, a recent study uncovered many similarities in the personalities of addicts, alcoholics, and criminals. Certain dif-

ferences were also revealed; on the rating scale used (the Minnesota multiphasic personality inventory), addicts cited many more psychopathic items and items dealing with social adequacy. Alcoholics, on the other hand, were found to be more preoccupied with religious matters, more hostile, showed more impairment of performance and more feminine characteristics than did addicts.

Tests using the Addiction Research Center inventory, an instrument for measuring subjective effects of drugs, showed that most drug effects could be defined by bipolar scales of "efficiency" and "reactivity." Preliminary data indicate that psychopaths tend to overestimate the most frequently occurring chance events and underplay the least frequent. Surprisingly, morphine appears to reduce the tendency to overplay the most frequent alternative. During a cycle of addiction to morphine, the basal conductance level of the skin increased as did the size of the electrodermal response to disturbing stimuli, suggesting a state of autonomic hyperreactivity during addiction. Similar studies are underway with pentobarbital.

Experimental psychology focuses on the psychological mechanisms associated with pain relief and the conditioning of narcotic drug effects in an effort to explain relapse. One study showed that suppression of the conditioned emotional response in rats by morphine was not due to a failure to perceive the conditioned stimulus or an inability to discriminate. The powerful drug etonitazene, when tested on rats, effectively suppressed abstinence from morphine and created addiction. Rats that are withdrawn from morphine drink more etonitazene than do control groups of rats; in other words the animals, once addicted, tend to relapse.

Biochemical studies

These studies, being conducted at the NIMH Neuropharmacology Service Center at St. Elizabeths Hospital, involve research in the effects of narcotics on chemical activities of cells within the central nervous system, as well as the development of improved methods for detection of narcotics in body fluids. Recent findings establish that catecholamine levels in the brains of addicted rats rise and fall to, but not beyond, normal concentrations during abstinence, indicating that addiction to and abstinence from morphine is associated with striking changes in catecholamine metabolism. The same phenomenon is being investigated to man through studies of catecholamine output in urine during cycles of addiction. Tests for detection of opiates in urine were improved during the year by changing from paper to thin film chromatography, which reduces analysis time from 24 to between 4 and 6 hours.

Neurophysiological studies

This area involves studies of changes in the central nervous system during addiction to opiates as well as research in activities occurring during cycles of barbiturate addiction in cats and dogs. Tests with dogs showed that tolerance and physical dependence upon morphine develop more rapidly in the brain than in the spinal cord, suggesting that more than one mechanism subserves these phenomena. The possibility that activation of parallel paths may be one such mechanism is currently being investigated, as are shifts in homeostatic regulatory mechanisms within the central nervous system. Further refinements have been made in the acute infusion technique which develops physical dependence in dogs in 8 hours. Using this method, investigators are testing patterns of reflex change in the spinal cords of dogs.

In other studies, chronically decorticated and chronically decerebellated dogs experienced withdrawal convulsions when barbiturates were withdrawn after chronic intoxication, indicating that neither the cortex nor the cerebellum is a necessary substrate for withdrawal fits. Future research will concentrate on the determination of thresholds for the elicitation of electrophysiological responses in various parts of the brain. Since drugs that are supposed to elevate gamma amino butyric acid levels in the brain have been shown to partially suppress abstinence fits, additional studies will necessarily involve direct measurement of GABA levels in the brain.

Detection of narcotics in the urine has been speeded by the use of thin-layer chromatography. This technique, which permits the rapid separation of various organic compounds, employs glass plates coated with absorbent material. The procedure is so rapid that the presence of narcotic drugs or their metabolites can be detected in the urine within 4 to 6 hours.

Application of this technique to narcotic detection in urine was studied and deemed feasible by scientists at the NIAMD, following a conference at Bethesda in which experts on addiction and opiate chemistry from several States agreed that better, more efficient methods than Nalline had to be developed for analyzing urine for opiate alkaloids.

In addition to its value as an improved method of detection, the technique is also believed to have potential importance as a deterrent factor when used as part of a followup program for paroled addicts. For example, a paroled addict who knew he would be subject to such a test might thereby have an additional reason for abstaining from the use of drugs. This is the theory behind the Colorado program previously mentioned.

EXTRAMURAL RESEARCH

Six mental health project grants relating to drug addiction were awarded during the year. One project, in East Los Angeles, will assist in the establishment and evaluation of a halfway house for narcotic offenders as part of the program of the California Department of Correction.

During the year, work proceeded under 23 research grants, 10 in the area of drug addiction itself and 13 which also covered other areas of study. The grants support a broad research attack on addiction, including these areas of investigation: neural mechanisms of psychopharmacological agents, biochemical basis of narcotic addiction, long-term assessments of the posthospital adjustment of addicts, development of a rapid test for narcotic excretion and tests of new drugs designed to block the addictive properties of morphine-type drugs without interfering with their desirable pain relieving effects.

TRAINING AND EDUCATION

The Institute provides support for graduate training in a number of mental health professions, in a systematic program to increase the trained manpower working in all fields, including such specialties as drug addiction.

The Public Health Service hospitals in Fort Worth and Lexington, and the NIMH Addiction Research Center at the latter, provide training in clinical care and research for psychiatrists and other medical personnel, nurses, psychologists, chaplains and students. Both institutions provide assistance and counsel to visitors from the United States and abroad who come seeking help in developing their own programs in drug addiction.

The amount and kind of information available to the public about drug addiction is woefully inadequate. Consequently, plans have been made to compile such information, as a roundup of present knowledge on the subject. At year's end, a mental health monograph on narcotic drug addiction was in press, at the Government Printing Office.

PROFESSIONAL ASSOCIATIONS

A report, "Narcotics and the Law," has been published by the American Bar Foundation, a legal research organization. The report consists of the organization's study of this country's experience in narcotic drug control.

The American Medical Association and the National Research Council of the National Academy of Sciences have studied the problem of drug addiction for a number of years. In May 1962 the two organizations issued a joint statement designed to correct widespread misunderstandings regarding the problems associated with drug addiction. According to the statement, the two groups support the following: (1) Followup treatment for addicts, after complete withdrawal, including services available at rehabilitation centers, (2) measures designed to permit compulsory civil commitment of addicts for treatment in a drug-free environment, (3) improvement of methods for rehabilitation of addicts under continuing civil commitment, (4) research into prevention of addiction and improved treatment of addicted persons, and (5) the dissemination of factual information about narcotic addiction.

Mr. LESINSKI. Mr. Chairman, may I, at this point, ask him a question?

Mr. FOGARTY. Yes.

ENGLISH DRUG ADDICTION PROGRAM

Mr. LESINSKI. Did you see the movie last night where they showed the English system of administering drugs to addicts?

Dr. FELIX. No, I did not, Mr. Lesinski. I know something of it but I did not see the show.

Mr. LESINSKI. Well, the program showed they may buy drugs as you would buy a prescription at the drugstore. They claim that there are only 460-some addicts in all of England.

Getting back to the statement you have made, that there is less apt to be a reoccurrence after 30, I think the reason for that is this. 'Youngsters go in for kicks, whereas the older person realizes the fact that he is hurting himself; that is why he is less apt to go back to drugs, after the person has matured.

Dr. FELIX. I have no doubt this is a factor in the case. There may be something happens physiologically, too, so that the cells in their body do not call for it.

Mr. LESINSKI. This fellow showed how he mixed the dope up, and how he administered it to himself. He was up to three grains, and he has used it practically all of his natural life, and it rather shocked me a little bit to watch this individual, watching him poke that stuff in his arm, but I just brought the subject up to show that it has been worked out, in the past.

Mr. FOGARTY. Is our hospital at Lexington full?

Dr. TERRY. We are filled there. As a matter of fact, we have a waiting list of some voluntary commitment patients who would like to come in there, who can only be taken as we get down on the waiting list.

Mr. FOGARTY. What about Fort Worth?

Dr. TERRY. The same thing is true there.

Mr. FOGARTY. Do you have a waiting list there, too?

Dr. TERRY. Yes, sir.

You see we have to give priority to the federally committed individuals, and second priority goes to the volunteer commitments.

Mr. FOGARTY. Tell us what progress you are making in schizophrenia?

Dr. FELIX. Could I add one more thing?

Mr. FOGARTY. Yes. Sure.

Dr. FELIX. I think a very important event happened this last year that should be brought to the attention of the committee officially, although we all know about it. In any event, that is the White House Conference on Narcotic Addiction this year, which, I think, increased public awareness a great deal; stimulated a lot more interest. We had more inquiries since then. I think it is rather significant that several different agencies and departments of the Government joined hands in their effort to try to attack this problem. This was not the Institute of Mental Health. This was the entire administration.

Mr. FOGARTY. One of the big problems, is preventing the drugs from getting into the country.

Dr. FELIX. That is right.

Mr. FOGARTY. Are we making headway there?

Dr. FELIX. The Narcotics Bureau states they are making headway.

SCHIZOPHRENIA

Mr. FOGARTY. Tell us about schizophrenia. A few years ago, you said that of all the mentally ill people in the country, about 50 percent were in this classification.

That varies though by age group, doesn't it?

Dr. FELIX. The age at which schizophrenia is more likely to attack is younger than it is for any other of the major mental illnesses.

The majority of the first admissions for schizophrenia in our hospitals—about three-fourths of such admissions, are between 15 and 44 years of age; where the age of other mental illnesses average about 51 years of age.

Now, this still accounts for more admissions each year than any other illness—about a fourth of all the patients admitted to public hospitals are schizophrenic, and about half of all of the patients in hospitals in any one day are schizophrenic.

There has been considerable improvement in what has happened to these patients after they have gotten in the hospital, over the last few years, due to these drugs. Several of the tranquilizers, particularly the phenothiazine groups, seem to be quite effective, in the cases of schizophrenia. There are three of the phenothiazines which have been found to sufficiently reduce the symptoms of a large proportion of schizophrenics, so that they can be cared for outside of the hospital, in their homes, and returned occasionally, for treatment—or more frequently, depending on their discharge—to the clinic for checkup and other therapy as it is needed.

We are working now to try to track down what may be the role of the pathological or toxic protein fractions in the blood of the schizophrenic which I mentioned earlier.

I mentioned that one of these studies is being carried on in Detroit. In 1964, we will expend about \$16 million, studying schizophrenia.

This is the largest single categorical area of the number of categorical areas which we single out for discussion before this committee.

SPECIAL REPORT

I am not sure whether this statement has been submitted or not.

Mr. FOGARTY. We have it, and will place it in the record.

(The special report follows:)

INTRODUCTION

Schizophrenia—still a scientific enigma—continues to pose one of the major challenges to the American health research effort. About one-fourth of the patients admitted each year to State mental hospitals are diagnosed as suffering schizophrenic reactions; 50 percent of the resident population of hospitals are schizophrenics. In economic terms, the high cost of schizophrenia arises from the fact that the disease has its greatest impact during the most productive years of life; data collected by the Biometrics Branch of the National Institute of Mental Health indicate that three-fourths of all first admission schizophrenics are between 15 and 44 years of age; the median age is 33 years, as compared with 51 years for all other mental hospital admissions.

As a reflection of the intensity of the NIMH effort aimed at the solution of the problem of schizophrenia, the following data—dealing with the Institute's research grant program—are revealing.

From the inception of the NIMH research grant program in 1948 until the end of fiscal year 1962, a total of 1,472 awards totaling \$40,833,599 were made for

projects in the area of schizophrenia; this represents 21 percent of the total number of grants and 28 percent of the total amount awarded to date.

Since 1948, annual support for studies of schizophrenia has kept pace with the overall growth of the research grant program; the number of research projects in the area supported through NIMH grants in fiscal 1962 was 30 times the number supported in 1948, and the amount awarded for studies of schizophrenia was over 90 times that awarded at the inception of the program.

The average award made through the NIMH research grant program for research in schizophrenia during the period 1948-62 was \$27,740—over \$8,000 greater than the average for the rest of the program.

This report provides a summary of the Institute's research activities concerned with schizophrenia, as well as those activities directed toward the appropriate utilization of new research developments in institutional and community settings in the field; a description is also furnished of efforts by NIMH to provide increased resources of trained personnel for both research and clinical work.

RESEARCH PROGRAMS

During the fiscal year 1962, over \$10 million was devoted to research activities in the area of schizophrenia, including relevant projects in the intramural program as well as awards made through the various Institute research grant programs. Over 270 projects relating to schizophrenia were supported through NIMH research grants during the year, with awards totaling nearly \$9.8 million; represented here are projects of various types—from small pilot studies in relatively unexplored areas to the diversified activities of large clinical centers.

Nowhere is the broad attack by NIMH on problems of mental health and illness better illustrated than in the area of schizophrenia. Consonant with the scope of the problem, schizophrenia research today encompasses a variety of sciences—including medical, biological, psychological, and social. Clues to prevention, etiology, and treatment are being sought in the chemistry of the body as well as in the quality of the mother-child relationship, in the mechanisms of the brain along with the social structure of the community, in the effects of psychoactive drugs and the dynamics of the patient-therapist relationship. The contributions of the biochemist merge with those of the pharmacologist, the findings of the anthropologist with those of the social psychologist; and often, members of highly divergent disciplines work together as members of a single research team.

The fields of study encompassed range from the most molecular of the biological sciences to the broadest of the behavioral sciences. Over one-third of the studies in schizophrenia supported through NIMH research grants during fiscal year 1962 were in the area of clinical psychiatry; one-fourth were in various areas of psychology—primarily clinical, physiological, social, and educational; nearly 10 percent was comprised of studies in psychopharmacology, 10 percent in biochemistry and physiology, and another 10 percent in sociology and anthropology. The remainder spanned a variety of additional areas—including, for example, public health, social work, nursing, history, and administration.

Half of the NIMH research grants in schizophrenia awarded during fiscal year 1962 were sponsored by colleges and universities; one-fourth were sponsored by hospitals (of these, half were State mental hospitals); and the remaining fourth by clinics, schools, health departments, and a variety of independent research, professional, and community service organizations.

The 500 investigators engaged in the study of schizophrenia under Institute grants reflect a broad, interdisciplinary approach. Forty percent were psychiatrists, and a fifth were members of other medical sciences including, for example, neurologists, pathologists, and pediatricians; a third were psychologists; and 10 percent were in the biological sciences—among them biologists, biochemists, and geneticists.

A wide spectrum of approaches are represented in the Institute's research program dealing with schizophrenia; the following subject matters covered in projects supported through NIMH grants during fiscal year 1962 are illustrative: brain function, 23 studies; endocrinology, 9; metabolic processes, 34; motor functions, 6; learning, 35; perception, 11; higher mental processes, 12; parent-child relations, 22; cross-cultural and acculturation studies, 7; language and communication, 7; social roles, 8; and attitudes, values, and beliefs, 10.

A substantive overview of the Institute's research effort in schizophrenia follows, including, where relevant, projects supported in the intramural as well as the research grant programs; unless otherwise noted, references are to projects supported through NIMH grants. While the groupings of projects under specific headings are sometimes arbitrary, they are presented to indicate the general scope of the research program in schizophrenia.

BIOLOGICAL FACTORS

The current state of biological research in schizophrenia is characterized by activity in a large number of disciplines, and the application of the newest techniques and concepts to the development and evaluation of a variety of hypotheses. Perhaps influenced by the sober and critical approach which investigators in the intramural program of NIMH have helped to formulate over the past 5 years, there are considerably fewer unsupported claims and unfulfilled promises of imminent breakthroughs and more attention to methodical, carefully controlled, and critical research.

Among the more cogent reasons for expanded interest in the biological factors in schizophrenia is the evidence for a familial or genetic tendency in the disorder. A statistical study of the incidence of schizophrenia in the families of schizophrenic patients, an examination of marriage and fertility patterns in schizophrenia, and studies of twins in the intramural program are examples of projects designed to elicit more reliable information than has hitherto been available regarding the relative importance of genetic factors in schizophrenia. In examination of the cells of schizophrenic patients, chromosomal abnormalities such as those which exist in certain forms of mental retardation have not to date been uncovered.

The possibility that the cells of schizophrenic patients are different from those of the normal population in one or another biological characteristic is being examined by studies of the enzymatic activities of human cells and by studies on cell permeability to sodium ion.

A considerable amount of effort is being devoted to exploring the possibility that a defect in aspects of body metabolism occurs in schizophrenic disorders. One investigator is involved in exploring the daily alterations in total energy metabolism in the body of schizophrenic patients and normal controls; in other projects, newer isotopic techniques are being applied in an examination of the metabolism of carbohydrate in schizophrenia, using glucose labeled with carbon 14.

The amino acids, in addition to their important role as the basic building blocks of protein in the brain and throughout the body, are of special interest in psychiatry because of the large number and variety of active agents which are derived from them. These substances—the amines—include such well-known hormones as adrenaline and noradrenaline, which have potent somatic and mental effects. They also include a vast number of substances in special places in the brain; these show alterations in their concentration in response to psychoactive drugs, and play an important role in behavior—including a possible role in schizophrenic behavior. The finding by scientists in the intramural program of a significant effect of methionine administration in some schizophrenic patients has led to an examination of the important process of biological transmethylation—whereby methyl groups are added to substances within the body—and a comparison of this process in schizophrenic and nonschizophrenic individuals. As a result of a major contribution by a scientist in the intramural program, the metabolism of adrenaline and related compounds within the body in various clinical conditions can now be investigated; a number of research teams in the intramural program as well as investigators supported through research grants are examining the possibility of an alteration in the production or metabolism of adrenaline and other catecholamines in various forms of schizophrenia and other mental disorders. Serotonin, histamine, and a number of other amines are being examined from the point of view of their metabolism or production and the possible relationships with schizophrenic illness.

Endocrine disorders are known to cause mental changes, some of which resemble those seen in schizophrenia, and examination of endocrine function in schizophrenics by recently developed techniques may reveal abnormalities not previously disclosed. A number of scientists—including investigators in the intramural program—are studying thyroid function, and the important interrelationships among the adrenal cortex, pituitary, the brain, behavior, and schizophrenia.

An approach which has been used for many years has been the search for a toxic factor in the blood or other body fluids of schizophrenic patients by observing the effects of such fluids on other cells or animals. In a number of current studies, investigators are pursuing this approach—examining the sweat of patients, or the blood for effects of a toxic factor on cells and tissue culture, or for its effects on resistance to stress and other aspects of behavior in lower animals. Some of these studies have confirmed the ability to distinguish—in the experimental test objects—certain cases of schizophrenia from a normal population. Considerable effort is being invested by a number of groups in an attempt to define a characteristic substance in the blood of schizophrenic patients; these studies are presently concentrating on the protein fraction of blood on the basis of preliminary evidence that a difference lies there. In addition to using modern techniques for protein fractionation, some investigators are applying newly developed concepts and techniques from immunochemistry which permit the demonstration and characterization of unique proteins in extremely small amounts.

Although the presence in a significant segment of schizophrenic patients of nonspecific electroencephalographic abnormalities has been known for some time, further exploration of this interesting facet of the disorder has awaited the development of more sophisticated techniques for analyzing and measuring the electrical activity of the brain in man; within the past few years such techniques have been developed, and they are now being applied in a number of advanced analyses of electroencephalographic activity in schizophrenic patients.

PSYCHOLOGICAL, SOCIAL AND CULTURAL FACTORS

Although many investigators view genetic aberrations as the *sine qua non* of schizophrenia—that is, as the condition which must be present for schizophrenic illness to occur—the role of psychological, social, and cultural factors in the etiology, course, and specific symptom formations of the disorder is regarded as crucial. The schizophrenic process can hardly be understood, nor can the schizophrenic patient be adequately treated, without recourse to such factors as childhood experiences, patterns of family interaction, and culturally determined attitudes and values; it is these kinds of psychological and social variables, many investigators are agreed, that produce the specific, learned behaviors seen among schizophrenics; that mediate the quality, quantity and content of the symptoms suffered; and—in the opinion of some—that actually trigger the occurrence of overt, frankly schizophrenic behavior, given the presence of genetically determined neurological and biochemical abnormalities.

In a number of studies, a variety of clinical insights regarding etiological factors are the bases of carefully formulated hypotheses now being subjected to rigorous tests. The importance of childhood environment in later development and adjustment, for example, has long been stressed in theory, or with the evidence of abundant case histories, but only recently—in a series of experiments with monkeys—have investigators provided the first important corroborative scientific evidence that inadequate rearing and traumas such as social isolation do, in fact, disrupt normal behavioral development and lead to difficulties comparable to the personality disorders and severe mental illnesses encountered in humans; it has been shown that infant monkeys who are separated from their mothers at birth and deprived of physical contact with other animals develop bizarre behavior patterns—from mute withdrawal to frenzied rage. The concepts and methods developed in this research have already been applied by several research psychiatrists and other behavioral scientists in clinical investigations of great importance in schizophrenia. One team has recently found that the adult monkeys that had been kept in complete isolation during infancy possess metabolic abnormalities similar to those found by some in schizophrenics, with comparable accompanying behavior—including fearfulness, withdrawal and inappropriate responses.

A number of projects are designed to study the impact of family experiences on the evolution of schizophrenic illness. In one study, investigators are initiating an experimental analysis of interaction among family members in order to test, in a controlled situation, a number of prevalent hypotheses about patterns of interaction and communication in families with schizophrenic members; by bringing the mother, father, and schizophrenic child into the experimental research setting, the investigators will be able to test some of the leading hypotheses regarding the schizophrenic family—nearly all of which have been derived from clinical, descriptive studies, without attempts to date at confirmation by the experimental method. Similarly, another team of social scientists is studying

how schizophrenia may be associated with attitudes developed as a result of the behavior of the patient's family. The interactions between patients and their parents in a problem solving situation are being analyzed and correlated with the patient's subsequent performance on specific tasks; the results will help determine what effects negative family interactions have on the schizophrenic's behavior. This study is typical of a number of projects in which the goal is a fuller understanding of the relationship between early life history and those inflexible and maladaptive adult responses which—in their more extreme and bizarre forms—constitute part of the symptom formation pattern in schizophrenia.

Although the role of the mother of the schizophrenic patient has frequently been given most attention, the nature of the total family structure as well as the pattern of relationships between parents has been the focus of more recent reports; according to these studies, a characteristic interaction pattern of parents of schizophrenic patients is one of greater dominance of one mate over the other than would be expected in a population of parents of non-schizophrenic offspring. In this connection, the purpose of one project was to investigate the reported association between the sex of the dominant parent and the adequacy of the premorbid adjustment of the schizophrenic son. It was found that paternal dominance was associated with good premorbid adjustment of the schizophrenic son, whereas in the case of those patients whose premorbid adjustment was poor, the mothers were dominant; the investigators reason that because of these differences in parental behaviors, it may have been somewhat easier for the sons with dominant fathers to learn the more usual adult male behaviors and therefore to achieve a somewhat higher level of maturity. It was also found that the parents of schizophrenic patients displayed more conflict in their interactions than the parents of other patients, and that this conflict was particularly marked in the parents of schizophrenic sons with poor adjustment prior to the onset of the schizophrenic episode.

In the intramural research program, it has now been demonstrated that the presence and even the specific form of schizophrenic disorder in a considerable variety of patients, both adults and children, can be deduced from a knowledge of the forms of thinking and patterns of communication found in other members of the family in which the individual patient has developed; in addition, it has been possible to match patients blindly with the families to which they belong, using projective test data and excerpts of personal interactions. The blind differentiations have been based on the theory that schizophrenia involves a breakdown or a developmental failure of certain essential psychological capacities which are ordinarily developed through the family environment—for example, the ability to sustain focal attention, to use language communicatively, to develop adequate modes of perception and interpersonal relationships, and to delineate fundamental roles for oneself.

A variety of leads are being explored in small pilot studies. In one project, for example, the investigator is studying autistic phenomena in congenitally blind children; careful observations of these children and their mothers might throw some light on the phenomenon of autism, for there is some evidence that autistic patterns in the congenitally blind result not only from the child's early experiential deficit, but also from the mother's inappropriate modes of adaptation to the child's plight. Another investigator is examining the family backgrounds and personal histories of a group of Catholic nuns suffering schizophrenic illness; in analyzing the relationship of the patients' psychiatric symptoms to their religious activities and attitudes toward their superiors, some general hypotheses regarding pathogenic factors may be crystallized.

The role of the social environment in schizophrenia is the subject of a number of investigations. One team is currently engaged in a followup of over 1,500 patients studied 10 years ago in a classic analysis of social class and mental illness. The project was conducted in New Haven by social scientists and psychiatrists to provide answers to two important questions in social psychiatry: Is mental illness related to social class? And, does a mentally ill patient's socioeconomic status affect how he is treated? To answer these questions, the investigators studied the social structure of the New Haven community, the psychiatric patients in treatment, the institutions where they are treated, and the individuals treating them. They found that while members of all social classes in the New Haven community are victims of mental illness, the predominant type of illness differs from class to class; the incidence of schizophrenia, for example, was much higher in the lower classes, and affective disorders and neuroses occurred more frequently in the upper class.

Moreover, each class reacted to the presence of mental illness among its members in different ways, and the treatment of psychiatric patients within the various classes differed accordingly—the family of the psychotic patient from the lower class displays more vehemently negative attitudes toward mental illness and psychiatric treatment than do the upper class families. Similarly, the investigators found that the type of treatment administered and the patient's responses to the treatment process were closely related to his socioeconomic status; patients from the upper classes were much more frequently given psychotherapy, while members of the lower classes were more frequently treated by somatotherapeutic techniques such as electric shock and hydrotherapy. The incidence of recovery and return to the community was higher for the upper classes.

This research dramatically revealed how necessary it is for the psychiatrist to consider and understand the social system of the community if he is to diagnose the patient accurately and treat him effectively. Now, in the followup study, it will be determined what proportion of the mentally ill individuals surveyed a decade ago remained in hospitals, died within a specified period after they first came under observation, or achieved specified levels of social adjustment in the community during the 10-year period; significant factors in the patients' histories—for example, age, sex, symptom formations, family and community environment—will be taken into account in attempts to assess their influence upon the course of each patient's illness. The results should lead to a better understanding of social and psychiatric factors operating in the success or failure of different types of treatment, and should help provide a factual basis for administrative planning of psychiatric services.

Another investigator is testing the hypothesis that at the lower class levels in the American urban environment, the degree of isolation and social disorganization associated with schizophrenia is greater for native Americans than it is for persons of Italian origin. In earlier research, relatively few schizophrenic patients in Naples were found to follow a steady course of deterioration; the investigator is now attempting to show that while the incidence of schizophrenia is higher in general among the lower socioeconomic groups, the presence of strong family ties—as exists, for example, among Italians—serves to buffer the stresses of social isolation and economic deprivation, and thus alters the course of the schizophrenic syndrome.

Within the intramural program, findings regarding family psychodynamics in schizophrenia are also being evaluated in a cross-cultural setting. In a small pilot study, it has been found that the criteria developed for evaluating projective test protocols obtained from diverse cultures; as a further approach to this problem, collaborative arrangements have been made with an investigator at the American University of Beirut in Lebanon, who will conduct family studies of schizophrenics under an Institute research grant.

EPIDEMIOLOGICAL STUDIES

Many etiological factors—including genetic as well as social—can be substantially clarified through carefully controlled epidemiological surveys which focus on the relationship between biological and environmental variables on the one hand, and the incidence of mental disease on the other.

One recently completed project—staffed by an interdisciplinary team of psychiatrists, psychologists, sociologists, anthropologists and statisticians—represents the first attempt to do an exhaustive epidemiological analysis of a highly complex and densely populated urban area. The initial volume of a projected three-volume series reporting the results of the research has been published; the book, "Mental Health in the Metropolis," represents a major contribution to the field of social psychiatry. The investigators used intensive psychiatric screening interviews to determine the mental health status of a large sample of adults residing in a 190-block residential area in Manhattan; in addition, a census was made of all persons living in the area who were under private, clinical or hospital treatment for mental or emotional disorders. The resulting data shed new light on the relationship between socioeconomic level on the one hand, and the incidence of mental illness and the availability of treatment on the other. The carefully collected descriptive data of this project—that is, of the actual incidence and treatment rates of mental illness in a major metropolitan area—are not only of general theoretical importance in the field of psychiatry, but also provide information with which to anticipate and plan actual treatment needs.

Another project is providing a picture of the ethnic distribution of mental disease in New York State. Analyses of the incidence of various types of mental disease among Jews and Negroes in the State, for example, will be the bases for hypotheses about the role of cultural, environmental, and genetic factors in the etiology of mental disorders. One investigator is conducting an epidemiological survey of first admissions to mental hospitals among northern native and migrant Negroes. Earlier findings showed that migrant Negroes were more heavily represented in first admission statistics than their distribution in the population warranted; more recent findings indicate that this finding is reversed for Pennsylvania. An intensive investigation of the Negro community in Philadelphia is now underway, with the aim of identifying some of the social and psychological factors responsible for the discrepancy.

Epidemiological surveys are of considerable importance, too, in a cross-national setting. One study of this type will provide an intensive followup of all first admissions to the Gaustad State Mental Hospital in Oslo, Norway, between the years 1938 and 1962—a total of 2,300 patients. Five clinical psychiatrists will visit all former patients in their homes, conduct careful psychiatric examinations, and make direct observations about the patient's social situation; the resulting data will be of special significance since Norway—with its nationwide system of registration for mental illness—provides many unique characteristics for a study in psychiatric epidemiology; all information from the national register is stored in a form amenable to automatic data processing cards, and the data are available for research.

An objective of another study is to learn whether the reported higher incidence of schizophrenia in certain areas in Croatia—along the Dalmatian coast and in the Istrian Peninsula—is in fact true. There appears not only to be a higher concentration of schizophrenia in these areas than in other parts of Croatia, but an unusually high incidence of all psychoses and of certain other diseases such as diabetes and rickets as well. Recent data suggests that the concentration may occur only within certain communities of the Istrian Peninsula; the investigators are now analyzing epidemiological data in the hope of shedding further light on some of the cultural and environmental correlates of schizophrenia.

CHILDHOOD AUTISM

Childhood autism is generally regarded as the earliest form of schizophrenia; it is also the most poignant, for it represents a portent of the waste and suffering of adult years to come. On theoretical grounds, autism in the young is seen by many investigators as a phenomenon which supports the concept of schizophrenia as a dynamic, developmental disorder.

One long-term project begun in fiscal year 1962 involves research, including longitudinal studies, on the etiology and epidemiology of childhood schizophrenia. The research team will continue some of its earlier work dealing with the development of neurologic and psychiatric criteria for the appraisal of schizophrenic children, and the analysis of prenatal and perinatal factors in the etiology of the disorder; the investigators will also initiate a number of additional projects, including a study of developmental changes in the treated schizophrenic child based on analyses of the features of the child and his family that correlate with clinical progress, and comparisons of the relative effectiveness of day and inpatient treatment. As another element of the overall project, the investigators will assess the families of schizophrenic children; their aim here is to collect information on the incidence of psychosis among the parents and siblings of schizophrenic children, and to test the hypothesis that the term "childhood schizophrenia" subsumes a heterogeneous group of patients with a complex etiologic spectrum ranging from somatic to familial factors.

The importance of gross cognitive and intellectual impairment in childhood schizophrenics has been noted by many. The literature concerned with the effects of schizophrenia on intelligence, however, although voluminous, is highly contradictory; a major problem is the lack of objective data on the premorbid intellectual ability of the schizophrenic. In one project, therefore, investigators have correlated measures of intelligence taken of children in the elementary school with similar measures taken more recently when, as adults, they became ill and were admitted to a mental hospital. Initial data point to the finding that certain progressive deficits in intelligence appear in children before they exhibit overtly schizophrenic symptoms; second graders who were not diagnosed as schizophrenics until adulthood were already significantly below their own siblings in intelligence.

The approach to child therapy of one team was based on the theory that children pass through three phases of development: the normal autistic phase—in which the infant has not yet become aware of anything beyond his own body; the symbiotic phase—in which the infant seems to become vaguely aware of the need for satisfaction from the outside, but in which the infant's mental image is still fused with that of his mother; and the separation-individuation phase—in which the infant gradually becomes aware of the separateness of his body and of his self. The investigators have postulated that some psychotic children have never developed beyond the autistic phase, whereas others have regressed from the challenge of separate functioning into a symbiotic-parasitic state; such primarily symbiotic children resort to autistic mechanisms as a defense against the anxiety which accompanies the symbiotic state. On this theoretical basis, the investigator has developed a form of therapy, involving both mother and child, that provides the child with a "corrective symbiotic experience"—that is, with a new and more mature relationship with the mother.

One of the challenges to those doing research in schizophrenia lies in the difficulty involved in reducing symptom complexes into meaningful diagnostic categories; a number of projects are directed at resolving this problem. One team has been engaged in attempts to clarify the difficult differential diagnosis between childhood schizophrenia and primary retardation among preschool, preverbal children; in addition, the differential responses to therapy of the two groups have been investigated. Before therapy, observations of the children at play and analyses of psychological tests revealed marked differences between the two groups. In their play, the retardates resembled the normals in their relations with persons, while they resembled the schizophrenics in their relations with objects; in contrast, the schizophrenics were severely impaired in their relationships to both objects and persons. Psychological tests revealed a greater variability in the intellectual functioning of the schizophrenics; the results indicated, too, that the schizophrenics are especially impaired in specific areas, including language and toilet training habits, while the retardates showed no specific disabilities. Results after a year of psychotherapy indicated significant gains for both the schizophrenics and retardates; contrary to expectation, the retarded children made more substantial gains. A control group comprised of schizophrenic children receiving no therapy showed evidence of regression.

In other projects, also focusing on more specific criteria for defining childhood schizophrenia, various investigators are developing methods for categorizing and coding data to permit more accurate diagnostic classification of psychotic children; systematically analyzing the speech characteristics of autistic children; and identifying precisely the day-to-day behaviors which accompany autism.

A number of studies in the intramural program have produced evidence that the parents of the schizophrenic child can be differentiated from the parents of the young adult who becomes a victim of schizophrenia. Projective test protocols from the parents of autistic children have been studied and compared with protocols from the parents of young adult schizophrenic patients. The parents of autistic child patients show forms of behavior—including openly sadistic and disaffiliating behavior—that would rebuff, impair, and interfere with the very beginnings of relationships they might have with the child. In contrast, relationships in the families of the young adult schizophrenics are not so totally shattered; here, rather, the focusing of attention and the achievement of coherent, integrated thinking is impaired, blurred and confused. The developmental process in the parent-child relationships of the autistic children appear to be disturbed more drastically and earlier than in the case for young adult patients.

It should be noted that one of the clinical research centers supported through the Institute and described in a subsequent section of this report has as its basic mission the conduct of studies in the etiology, pathogenesis, clinical phenomenology, and efficient therapy of the young schizophrenic child.

TREATMENT AND PROGNOSIS

The search for new and more effective techniques for the treatment of schizophrenia continues concurrently with attempts to understand its causes and to initiate methods of prevention. In the area of psychopharmacology, the past few years have seen a series of converging findings that have served to demonstrate the effectiveness of potent phenothiazine drugs in the treatment of schizo-

phrenic reactions. The drugs—including, for example, chlorpromazine, perphenazine, prochlorperazine, triflupromazine—have been used with success in treating manifestations of acute schizophrenia such as excitement, hostility, confusion, paranoia, hallucinations, bizarre behavior, disorganization of thinking, and withdrawal; a number of the drugs have also been found to be useful in the treatment of chronic schizophrenics hospitalized from 2 to 10 years. Such studies have provided scientific support for the usefulness of drugs in returning patients to the community, and in reducing the chances of relapse and rehospitalization. Even the seriously ill, relapsing patient can avoid rehospitalization, results show, with a combination of phenothiazine drugs and a day-care program.

More recently, with the development of sharper diagnostic subcategories, investigators have begun to identify the relative effectiveness of given drugs among specific types of patients. In one investigation, for example, two tranquilizing drugs—acetophenazine and perphenazine—were compared on a sample of newly hospitalized schizophrenics. Although general improvement was noted among all patients, acetophenazine was found to be clearly the more effective drug in patients classified as paranoid, while perphenazine was considerably more effective among nonparanoid patients.

A variety of studies focus on psychotherapy in the treatment of schizophrenia. Work continues on the analysis of data from one study in which the relative effects of four different procedures in the care of schizophrenic patients of relatively good prognosis are being evaluated: psychotherapy, drug therapy, electroshock therapy, routine milieu therapy, and drugs combined with psychotherapy; in another project the investigator is seeking to determine how the amenability of children to treatment is affected by the climate of the institution; one team continues to seek answers to questions regarding the differential effectiveness of more or less intense therapeutic treatment; and, many investigators are studying the basic psychodynamics of therapeutic procedures in order to throw light on those specific aspects of the therapist-patient relationship that facilitate the healing process.

In one study—a 5-year followup study of adult psychiatric outpatients—it was found that improvement immediately following treatment was primarily in relief from anxiety and depressive symptoms; after 5 years, all types of symptoms were substantially reduced. Patients found to be most improved after 5 years were younger than others and had been more seriously sick initially; those least improved suffered many somatic symptoms, both initially and after 5 years. At the end of 5 years the least improved patients were found to be more likely than the others to define their illnesses in bodily terms, or to express them ambiguously. Consistent with this, the least improved patients sought more and different kinds of treatment resources, which, in turn, may have aggravated their condition by increasing their confusion. The investigators have shown that ability to respond to treatment may be a function of the patient's success in communicating his difficulties to his therapist, and of the acceptance by both patient and therapist of a course of action.

The choice of an appropriate course of treatment in relation to specific diagnostic and evaluative categories is, in fact, one of the major scientific problems facing psychiatry today; psychiatry is the only branch of medicine which does not have diagnostic laboratories reporting their results in the dimensions of natural science. The goal of one project, therefore, is to provide a basis for culture-free, automatic, laboratory measures of the behavioral excesses and deficiencies which characterize the psychoses; the strategy here is to accomplish this goal through simple laboratory tasks adapted from clinically relevant behaviors, and the methods developed to date have, in fact, been found to correlate highly with other diagnostic criteria. The advantage of the system under development is that it is possible to have systematic behavioral measurements and evaluations conducted by intelligent technicians with little formal education, thus relieving professional staff for other duties, for example, the selection of therapies and actual treatment; the automatic property of the system also removes the interpersonal aspects so much a part of usual diagnostic techniques, and permits the changing of diagnostic and evaluative personnel without introducing individual differences in evaluative bias.

A number of investigators are concerned with the problem of anticipating and predicting the course of schizophrenia among hospitalized patients subjected to various therapeutic measures. The results of one study indicate that factors associated with favorable outcome reflect a history of effective adaptation prior to the onset of illness; among the positive indices are marriage, extroversion,

good social history, and good premorbid adjustment. Also related to favorable outcome are such factors as sudden onset, demonstrable precipitating factors, and a duration of illness of less than 2 years. Such findings serve to clarify the treatment approaches that might be taken with individual patients suffering schizophrenic illness.

For some years, a major focus of the Institute's intramural program has been the study of family psychotherapy, in which parents, their young adult or late adolescent offspring, who are the patients, and the siblings of the patients are seen together, usually twice weekly. On the basis of substantial experience with family therapy, the intramural staff is now formulating ideas about technique, indications, and contraindications for this new and important, but complicated treatment method. Individual psychotherapy and casework, family art therapy, and naturalistic home visits have also been significant sources of clinical observations in the family studies of the intramural program.

Although investigations are being conducted at a number of clinical research centers to evaluate various forms of treatment used with the schizophrenic patient, one center will have as its central interest an objective study of the psychiatric treatment process. The range of investigations will include studies of the biochemical, psychophysiological, social and psychodynamic changes associated with therapy of various types, as well as the study of those patient characteristics which mediate improvement during treatment; equal attention will be given to factors in the total social context which affect the patient's response to treatment.

DESCRIPTIVE STUDIES

An analysis of the Institute's research grants in schizophrenia in terms of the primary clinical goals of the research reveals the following distribution: A third are studies of treatment; 10 percent of the studies are concerned with developing improved diagnostic procedures; another 10 percent are devoted to problems of care and rehabilitation; nearly 10 percent involve studies of problems of etiology, epidemiology, prognosis, and prevention; and finally, the largest proportion, nearly 40 percent while they overlap with other goals, can best be classified as descriptive studies, devoted to increasing our knowledge about the symptoms, syndromes, manifestations, course and evolution of the disorder.

These data clearly reflect the present state of our knowledge of schizophrenic illnesses; we are still today in good measure at the first, rudimentary level of scientific inquiry—the phenomenological level. It is important to note, however, that with increased research sophistication and with steadily increasing funds of knowledge, descriptive data are becoming more rigorous and more immediately available for purposes of understanding the etiology of schizophrenia and of initiating measures of prevention and treatment.

In the area of cognitive and verbal processes, for example, scientists are gaining a fuller description and understanding of schizophrenic processes. The importance of these studies stems from the fact that in contemporary society, most contacts with others are maintained by means of verbal behavior; in schizophrenia more than in normal states the individual is known more often by what he says than by what he does, and one of the central aspects of schizophrenia posited by workers in the field has been its characterization as a thought disorder.

Investigators recognize a need for a delineation of the variables which control the patient's verbal behavior as well as its interpretation by the clinician. Some of the variables being studied are related to the syntax of the patient's language, some to the attitudes and values of the patient, some to the behavior of the interviewer or tester who elicits the verbal behavior, and some to the pathology of the patient. In one study, investigators have devised an experimental situation which mimics a psychoanalytic setting. They are analyzing patterns of free association to identify the degree to which the patient's personality influences the way he responds to the free association process; here, nonpsychotic individuals are being compared with schizophrenics in their associative thought processes.

In a number of studies, investigators are using the theoretical framework of operant conditioning to investigate speech patterns of schizophrenics and to explore variables and techniques by which to modify them. One investigator, for example, is attempting to determine whether it is possible to condition withdrawn schizophrenics to speak more, and rambling schizophrenics to speak less; the investigator is trying to promote verbal communication in psychotic patients

by reinforcement, using certain rewards like cigarettes, or candy in the case of young children. The importance of being able to elicit or control verbal behavior would be crucial in therapeutic procedures. The research of another investigator focuses on specific aspects of speech like lengths of pauses and communicability, and how these can be conditioned; in still another study, a spectograph is being used in order to analyze the frequency spectra of speech among various types of individuals and among the same individuals whose emotional and physiological state varies over time. Among the exploratory studies being pursued in this area are, for example, attempts to study thinking deficit in schizophrenics as a function of emotionally disturbing situations, and the social variables which distort the concept formation of schizophrenics and act as distractors to normal thought processes.

In the area of social and interpersonal behavior, many investigators are seeking to develop rigorous descriptive data to provide a deeper understanding of the patient's private world. In the literature of the helping process, for example, one investigator reports a lack of systematic, natural descriptions of the whole range of immediate complaints that are faced by the staff of a psychiatric facility; such descriptions would offer a means for differentiating the immediate sources of the difficulty in current family and interpersonal relationships as distinguished from long-term psychodynamic considerations. The investigator is therefore engaged in a pilot project designed to describe and evaluate the complaints presented to a clinic viewed in terms of what can be done in the social and family situation immediately to prevent hospitalization. The investigator's ultimate goal is to establish the specific parameters for a well-designed home-care program directed toward the amelioration of the immediate stresses that threaten to require a patient's hospitalization.

Another project has as its goal to compare schizophrenic and normal performance in games requiring some degree of interpersonal coordination. A number of clinical theorists have proposed that at the core of the schizophrenic disorder is a massive inability to exchange meanings or to achieve a reliable degree of coordination of thought with others. The investigators want to determine to what extent schizophrenic communication represents a generalized deficit in intellectual ability, as compared with the extent to which it reflects a disorder in the specific mechanisms necessary for adequate communication. Their studies are aimed at assessing a variety of processes, including role-taking, metacommunication, social motivation, and facets of intellectual ability; it is expected that some light can thus be shed on the relative contribution of such factors to the communicative pathology associated with various classes of schizophrenia.

A continuing aspect of the Institute's intramural research program concerns the social relations of mental hospital patients with special emphasis on the lack of sociability manifested by chronic schizophrenics. Research with chronic schizophrenics has been directed at exploring the motivation behind their apparent aversion to social interaction. Earlier findings indicate that chronic schizophrenics have a capacity for social behavior that is not generally recognized or exploited in treatment; their capacity is blocked, however, by a fear of being placed in a position in which they might be called upon either to give or to receive expressions of feeling. Important differences have been noted between male and female patients, and newly inaugurated work is designed to compare male to female patients both with respect to their behavior on the ward and with respect to the relationship of ward behavior to internal psychological functioning.

In further experimental work, investigators in the intramural program have attempted to assess the effect on schizophrenics' level of functioning, of being able to affect the fate of another individual either positively or negatively. The results suggest that the variation in performance among patients in such a situation is substantial, and seems to be a function both of the type of illness and of culturally defined sex roles. Over the course of time, however, the hospital environment appears to deemphasize initial differences between patients in different diagnostic subcategories so that the behavior of all patients eventually tends to conform to a common norm. Thus, among male patients, the catatonics are initially more hostile and the paranoids more benevolent; in time, the catatonics become more benevolent and the paranoids more hostile. Reverse trends occur among the female patients, catatonics being initially more benevolent and paranoids initially more hostile. This leveling effect of hospitalization supports the contention that the environment of large mental hospitals deemphasizes individual differences among patients.

Investigators are seeking, too, to provide better description data regarding the sensory and perceptual experiences of schizophrenics. Rigorous tests and laboratory procedures are being devised in one project to test for visual impairment among schizophrenics including deficiencies in acuity and dark adaptation. Ophthalmologists and psychiatrists have long recognized the psychogenic origin of many visual disturbances in neuropsychiatric disorders, and the investigators' work will shed additional light on this phenomenon. Another research team is engaged in an investigation of affective processes among schizophrenics through their perceptions of the human face. The investigators are determining whether there is a relationship between the affective states that accompany particular psychopathological disorders, and the perception by patients of emotion in the facial expressions of others.

Much needed, too, are more ample descriptions of specific pathologic phenomena. One investigator, for example, is studying the correlates of hallucinatory activity in paranoid schizophrenics by recording, during hallucinatory experiences, subvocal language behavior as well as muscle movements from the lip, chin, and laryngeal areas. Pilot work using a microphone indicates that it is possible to hear and understand the subvocal speech of an individual reading silently to himself with no lip movement; hence, it is conceivable that hallucinations can be controlled by controlling laryngeal activity through nerve blocks, drugs, or external stimulation applied to the throat.

Studies of the type noted in this section—all of which are intended to describe rigorously the parameters of deficit performance and pathological behavior of schizophrenics—will assist in identifying the nature, and perhaps one day the locus, of the disorder.

METHODOLOGICAL STUDIES AND LITERATURE SURVEYS

Behavioral scientists engaged in research on schizophrenia continue to use those research techniques, analytic methods, and psychological tests and measurements available to them. At the same time, however, a number of investigators are attempting to sharpen existing methodological approaches, and to add to the arsenal of research weapons available in the field.

One of the most difficult problems posed in research involving the mentally ill is that of making accurate measurements of the patient's overt behavior, his degree of psychopathology, his change as a result of treatment, his symptom patterns. To meet this challenge, some investigators are directing their efforts toward the development of new rating scales, others toward the refinement of existing ones. In one project objective measures are being devised for a variety of specific aspects of patient behavior. Another study is resulting in rating scales for use by personnel at various levels, from low-level attendants to highly trained professionals; such scales will permit evaluations to be accomplished by those closest to the patient throughout the day in a variety of contexts. In still another project the investigator is adapting rating scales originally intended for use with acute patients so that they can be applied in assessing changes in chronic patients as well.

The development and standardization of psychological tests which probe beyond overt behavior into the psychodynamics of personality functioning continues to be crucial. Among the relevant projects here is one aimed at establishing the reliability of a word association test when used with schizophrenics, and others intended for the development of a new projective ink blot test; a test of ability to reason through analogy; and tests of the patient's efficiency in performing tasks involving reaction time and conditioned responses.

New resources and approaches for data analyses are constantly being sought. One team is evolving new and rigorous bases for correlating aspects of family relationships with specific symptoms of schizophrenia; another investigator is preparing electronic computer programs to permit large-scale analyses of clinical psychiatric data. In one project a team is at work maintaining a rich source of psychological test data taken of 15,000 ninth grade children in Minnesota 13 years ago; the data are being kept current for the purposes of longitudinal, etiological studies that will be free of retrospective reporting.

Although analyses of pertinent literature are a basic ingredient of most studies, some projects are devoted wholly to the review of specific information in the field. One specially qualified investigator, for example, is translating all of the Russian literature dealing with a variety of problems in the mental health field—including the care and treatment of schizophrenia and the major psychoses.

CLINICAL RESEARCH CENTERS

The clinical research center program is the basis of support for research organizations with sound, integrated research programs which are directed toward the comprehensive investigation of problems related to mental health and illness. Research centers of this kind are intended to provide a stable organizational framework in which investigators who are engaged in a large-scale attack on problems of mental health can enter into effective collaboration in an atmosphere of common purpose; here, efforts in diverse scientific disciplines are integrated and focused on a goal relevant to the solution of the problems of mental illness. The intellectual environment provided in such a setting will, it is hoped, create exceptional opportunities for the germination and cross-fertilization of ideas, and will provide investigators with opportunities for long-term careers in the mental health field.

Of the seven grants awarded for mental health clinical research centers during fiscal year 1962, four were for research centers engaged in broad investigations of schizophrenia; awards totaled nearly \$1 million. More recently, support of an additional center was initiated to study the etiology of schizophrenia in a State mental hospital setting.

Those centers engaged in research on schizophrenia provide the opportunity, within a hospital or clinic setting, to establish a research ward in which studies by investigators from a variety of disciplines, ranging from biochemistry to social psychiatry, can intensively study patients in a controlled environment. The centers now being supported plan extensive studies to describe in a detailed and continuous fashion the biological, psychological and social characteristics of schizophrenic patients; such observations are not possible in the typical hospital ward or clinical setting. Multidisciplinary studies of etiological factors in schizophrenia are being conducted. These studies include the collection of genetic, physiological, biochemical, psychological and social background data; the unique settings provided by the clinical research centers will enable the investigators to correlate their data with changes and fluctuations in the patients' behavior during treatment.

RESEARCH UTILIZATION BRANCH

The Institute's Research Utilization Branch, formerly known as the Community Services Branch, functions as a link between the research laboratory and field demonstrations on one hand, and those agencies and groups responsible for developing and conducting mental health service programs on the other. As its name implies, the branch provides varied professional and technical support, including assistance in the development of integrated and comprehensive State and local mental health programs; stimulation for the process of translating research findings into operating programs; and encouragement for the development of new ways of providing services for the mentally ill as well as new methods of meeting community mental health needs.

Staff members of the Research Utilization Branch are available for consultation with State and local organizations and with appropriate national agencies, both public and voluntary, to assist in the development of coordinated, cooperative programs and services to meet current and future mental health needs. Branch staff also stimulate the development of mental health project grants, technical assistance projects, and pilot and demonstration projects covering a full range of services to the mentally ill.

In relation to the public health problem of schizophrenia, the Branch staff—utilizing all of the programing resources available to them—focus their activities primarily on the resolution of the following problems: How can the newly admitted patient be prevented from developing into the long-term chronic patient? How can the hospital experience be made therapeutic for the patient rather than custodial? And, how can chronic patients be sufficiently resocialized and rehabilitated to return to a useful life in the community? In stimulating new and improved treatment modalities and techniques within the mental hospital, and in encouraging the development of community mental health services for the diagnosis, treatment, and rehabilitation of the mentally ill, it is hoped that a "circle of services" will be provided to avoid hospitalization for long periods of time, or to make hospitalization altogether unnecessary.

Since schizophrenic patients constitute a large proportion of the mentally ill both in hospitals and in communities, the research programing activities of the Branch reflect emphases in both areas. About one third of the mental health

project grants are related in some degree to problems of the treatment and rehabilitation of schizophrenics. Projects in Massachusetts, New York, and Illinois involve the development of day nursery, day hospital, and educational programs for schizophrenic children; family-centered treatment in schizophrenia is being demonstrated in North Carolina, Pennsylvania, and California; in New York City, a team is studying the effects of a continuous comprehensive treatment program for schizophrenia; in Massachusetts a study is being made of interpersonal relations and rehabilitation of married male schizophrenics after hospitalization; in Kansas, a study is being made of the feasibility of a treatment program for chronic schizophrenics in which the aid-patient relationship is the primary treatment instrument of the hospital team.

The importance of both hospital and community care is reflected, too, in the program of technical assistance projects. During fiscal year 1962, two such projects concentrated on the problem of sharing information and program experiences in improving patient care in the hospital. Others focused on discussions of the broad range of services that make up comprehensive after care programs for mental hospital patients. In addition—building on the dramatic and successful experiences in using volunteers in therapeutic activity within a hospital setting—one technical assistance project was directed toward the college-student companion program, and another was designed for administrators of volunteer service programs in State mental hospitals.

Special attention was also given in all Branch activities to the development of preadmission and supportive, community followup services such as emergency services, halfway houses, ex-patient clubs, day and night hospitals, psychiatric units in general hospitals, foster and family care plans, and after-care clinics. Since the ultimate objective of those activities is to enable patients to return to the community to lead personally satisfying and socially productive lives, the Research Utilization Branch's program activities involve continuous liaison with a variety of agencies within the Department of Health, Education, and Welfare.

BIOMETRICS PROGRAMS

As part of its total program, the Biometrics Branch is engaged in measurements of the prevalence and incidence of mental disorders, and the relating of this information to pertinent factors of demography, sociocultural environment, and treatment programs. In conjunction with this function, the Institute's biometrics program provides consultative and direct services to State and local departments of mental health. The Branch also supports a long-range program to improve and coordinate the flow of statistical data from various sources in the United States.

The expansion of the newer treatment methods—including day, night, and open hospitals, and the use of drugs—has led to increased complexities in the interpretation of statistical data, and has emphasized the need for new statistical reporting systems of adequate scope and flexibility. A model reporting area, in which mental health statistics are processed each month, now includes 30 States. Cohort studies of the fate of schizophrenic admissions, among other patients, have shown wide interstate variations in release, retention, and death rates, as a function of hospital policies. Through a refinement of cohort studies, Branch staff members are now attempting to control some of the variables which contaminate the comparability of such data.

Through the national reporting program on outpatient psychiatric clinics, data are also available on services to schizophrenic outpatients. Approximately 3,000 patients under 18 years and 17,000 patients 18 years and over discharged from 931 reporting clinics in 1961 (59 percent of the 1,589 clinics in the country) were classified as suffering a schizophrenic reaction. This represents only 6 percent of the patients under 18, but 22 percent of the patients 18 and over diagnosed as suffering a mental disorder. In a comprehensive study in Maryland conducted by the Institute, it was possible to compute rates of discharge from clinics per 100,000 population.

Nationally reported data indicate that in 1960 nearly one-quarter of all first admissions to public mental hospitals were patients with schizophrenic reactions. Half of the patients resident in the public mental hospitals in 1960 were schizophrenic. Their median age was 49 years as compared with 61 years for all other resident patients; almost half of the schizophrenic resident patients were aged 45–64 years.

Not only are biometric data of the kinds noted here of importance in sensing the distribution and flow of types of mental disorder under various conditions,

but it is probable that comparative data will further the refinement and standardization of present day clinical, diagnostic techniques.

TRAINING

The Institute's support for the training of professional personnel in skills relevant to schizophrenia is maintained as an integral part of the training grant program in psychiatry, psychology, biological and social sciences, social work, and nursing. In addition, a large share of the Institute fellowship program supports the training of scientists in research skills associated with the understanding and treatment of schizophrenia; predoctoral and postdoctoral fellowship programs designed to support the basic and early training of scientists in mental health research fields have been amplified in recent years by fellowship programs intended to provide support for increasingly higher levels of research training, to assist in the establishment of stable research positions, and to meet specific research training needs in various problem areas like schizophrenia.

SUMMARY

This paper provides a summary of the current activities of the National Institute of Mental Health devoted to the solution of the problem of schizophrenia; the studies cited are intended as illustrative rather than as an exhaustive representation of the program.

While most of the studies described here are quite clearly related to specific schizophrenic phenomena, it must be emphasized that the eventual understanding of a complex disorder such as schizophrenia will depend not only on an exhaustive exploration of the schizophrenic process itself, but, more important, on an accumulation of knowledge regarding the fundamental mechanisms involved in the brain and in behavior. The causes of schizophrenia are still unknown, and the pathogenesis of the disorder undoubtedly involves complex interrelationships within the nervous system, and interactions among the nervous system, various other organ systems of the body, and the interpersonal relationships of individuals; basic information from a variety of sciences is, therefore, of prime importance. Basic research on normal thought processes, for example, is essential to an understanding of abnormal thinking, and fundamental knowledge of normal metabolism and of the biochemistry of the brain is essential to a comprehension of the ways in which these processes may be defective in a disorder like schizophrenia. It can be stated with some confidence that when the final chapter in man's understanding of schizophrenia is written, the great bulk of the contributions which will have led to that achievement will have come from basic research of the type noted above—work which is in fact research in schizophrenia, even though it cannot be designated as such at this time by the scientists themselves or by anyone reviewing their efforts.

There are no assurances on the basis of current research that the schizophrenic illnesses which have challenged the best scientific minds for 2,000 years will be solved within the next year or two. There are, however, a gratifying number of new and interesting observations of considerable potential significance which demand further exploration; fortunately, an increasing number of competent investigators are interested in exploring them.

INCREASE FOR RESEARCH GRANTS

Mr. FOGARTY. By far, the largest increase in your budget is \$25,120,000 for research grants.

The Bureau of the Budget treated you considerably different than the other institutes in that you are going to finance over 500 more new grants in 1964 than you are in this year.

Is that right?

Dr. FELIX. That is correct, sir.

Mr. FOGARTY. And if you had more money you perhaps could finance more.

Dr. FELIX. That is probably so, although in my best judgment, my professional judgment, this is a good, sound budget and I do not think it is too little or too big.

Mr. FOGARTY. What was your original request?

Dr. FELIX. While I am finding it here, I would like to make one comment.

Mr. FOGARTY. Research grants, I am talking about now.

Dr. FELIX. Here it is. I would like to point out one thing about this request before I give you the figures, Mr. Chairman.

At the time that we were called upon to make our original estimates, I had asked the Department if it were possible that I not submit an estimate at this time, because everything was pretty much up in the air.

The President appointed an Interdepartmental Committee to study the recommendations of the Joint Commission on Mental Illness and Health, and to come up with recommendations. We were in the midst of this. I did not exactly know where this would go.

I was told by the Department and I can understand their position, that this would leave the whole departmental budget open, since they would not have the Institute of Mental Health budget; so I did the best I could and submitted an estimate with the full knowledge and with the information being given to the Department, that this budget was not as accurate as it could be had I had information that was not yet available.

Now, with that information—so that you will know that this does not mean that this is the wisest estimate that could be made, as of today—

Mr. FOGARTY. Let's talk about as of today.

Dr. FELIX. As of today, I would stand on the research grant estimate provided for in the President's budget of \$80,755,000.

Mr. FOGARTY. The same thing for research grants?

Dr. FELIX. The \$25 million increase; yes, sir. I would say that is a good budget.

SPECIAL PROJECT GRANTS TO INSTITUTIONS

Mr. FOGARTY. Are you starting a new program, or new type of grants, or is this just an extension of your current program?

Dr. FELIX. The principal new type of grant here is the one that was discussed earlier today.

Mr. FOGARTY. The \$100,000 for mental institutions?

Dr. FELIX. Up to \$100,000 to the institutions for the mentally ill and the mentally retarded.

This will be carried out if the money is appropriated under the authority contained in the so-called title V which is now section 303, I believe, of the Public Health Service Act.

Mr. FOGARTY. Well, will you prepare for the record, a statement on the background for this and the legal authority?

Dr. FELIX. I would be happy to, sir. Yes, sir.

(The requested statement follows:)

MENTAL HEALTH PROJECT GRANTS TO STATE INSTITUTIONS FOR THE MENTALLY ILL AND THE MENTALLY RETARDED

LEGISLATIVE BACKGROUND

The mental health project grants program was authorized by title V of the Health Amendments Act of 1956, (Public Law 84-911) and the first grants under this program were made in 1957.

This legislation made possible the awarding of grants to State mental hospitals, as well as other organizations, for " * * * investigations, experiments, demonstrations, studies, and research projects with respect to the development of improved methods of diagnosing mental illness, and of care, treatment, and rehabilitation of the mentally ill, including grants to State agencies responsible for administration of State institutions for care, or care and treatment, of mentally ill persons for developing and establishing improved methods of operation and administration of such institutions."

Further this legislation requires that these grants be made only upon favorable recommendation of the National Advisory Mental Health Council.

Through the years approximately 115 grants have been made to State institutions for the mentally ill and for the mentally retarded under the provisions of title V (Public Law 84-911).

As there are 279 State institutions for the mentally ill and 108 institutions for the mentally retarded, it can readily be seen that the number of grants awarded is very low. Thus, the Federal Government has been playing a relatively modest role, although an important one, in assisting the States to improve their State institutions for the mentally ill and the mentally retarded.

SUBSEQUENT DEVELOPMENTS

In 1955, the Congress enacted legislation which has had an enormous impact upon the people of this country, and which in future years may well be considered one of the keystone acts in the field of mental health and illness. This was the Mental Health Study Act of 1955 (Public Law 84-182) which provided for an "objective, thorough, and nationwide analysis and reevaluation of the human and economic problems of mental illness."

In order to carry out the study called for in that legislation the Surgeon General awarded grants to the Joint Commission on Mental Illness and Health. The Joint Commission was comprised of members of the leading professional organizations in the field and was financed in part by the National Institute of Mental Health. The final report of the Joint Commission on Mental Illness and Health which was transmitted to the Congress by the Joint Commission in the spring of 1961, represents the most intensive study of the problems of mental illness and health undertaken in this country in the last hundred years.

In December of 1961 the President directed the Secretary of the Department of Health, Education, and Welfare to consult with the Secretary of Labor and the Administrator of Veterans' Affairs in the preparation of recommendations for broadened Federal activity in the field of mental health. An intensive review of the Joint Commission report was conducted and in December of 1962 the findings and recommendations of the committee were reported to the President.

THE PRESIDENT'S PROGRAM

On February 5 of this year, the President, in an unprecedented action, transmitted to the Congress his special message on mental illness and mental retardation. In this message the President said:

"I propose a national mental health program to assist in the inauguration of a wholly new emphasis and approach to care for the mentally ill. This approach relies primarily upon the new knowledge and new drugs acquired and developed in recent years which make it possible for most of the mentally ill to be successfully and quickly treated in their own communities and returned to a useful place in society."

The President in his message proposed essentially a 5-point program:

1. The provision of Federal assistance through planning grants for the development of comprehensive mental health programs by the States.
2. The establishment of comprehensive community mental health centers through the provision of Federal support on a sharing basis for construction and early year operation.
3. The provision of special grants for demonstration projects to assist State mental hospitals to improve the quality of care, and to provide in-service training for personnel manning these institutions. This will permit the hospitals to perform a valuable transitional role, through the strengthening of their therapeutic services, and by becoming open institutions serving their local communities.
4. The expansion and extension of efforts to increase the supply of and improve the utilization of trained manpower.

5. The support of expanded research in order to "push back the frontiers of knowledge in basic and applied research into the mental processes, in therapy, and in other phases of research with a bearing upon mental illness."

The basic premise underlying the President's program is the conviction that if the Nation effectively utilizes what is now known about the mental illnesses it is possible, within the next 25 years, to see the disappearance of the State mental hospital as it is known today. Until community mental health programs fully develop, the quality of care in existing State mental institutions must be improved. The Federal Government can play a significant transitional role by encouraging State mental institutions to undertake intensive demonstration and pilot projects to upgrade the quality of care and to provide inservice training for supportive personnel. The proposed hospital improvement and inservice-training grants are designed to achieve this important goal.

THE STATE MENTAL HOSPITAL SITUATION

State mental hospitals for a considerable period have reflected a public sentiment that once mentally ill, an individual was doomed to a hopeless existence with little or no prospect for partial or complete recovery. As time has progressed, however, enlightened and more humanitarian and hopeful approaches to the solution of the problems of the care, treatment, and rehabilitation of the mentally ill have become manifest. As a result, many patients previously thought to be hopelessly ill now may be treated successfully and return to live in the community.

Although the public mental hospitals have made a major contribution to the accomplishments realized, they have not attained the status of which they are capable, nor have their outstanding accomplishments become widespread among hospital systems.

During the 1930's the State hospitals were beset with problems of overcrowding, drastic reductions in budgets, and difficulty in releasing patients as a result of the inadequacy or unavailability of other supportive institutions or agencies. Owing to financial circumstances, the cessation of building programs in many States, and the shortage of hospital beds, such overcrowding was acute.

Before the State hospitals were able to recover from the financial setbacks and deterioration experienced during the 1930's, they were struck by another severe blow. World War II accentuated many of the continuing problems and bled the State hospitals of their never plentiful professional personnel and financial resources.

However, after the war years, improvements gradually began, and significant progress had been achieved by 1953, when more than a half billion dollars a year was being spent by the States for mental hospitals alone—an amount three times that which they were spending just 9 years before in 1945. During the same period, as staffs were enlarged and salaries increased, salary and wage expenditures rose from \$89 million to \$320 million, an almost fourfold increase; and within certain individual States, expenditures for salaries and wages multiplied six or seven times.

Despite these improvements, the States continue to face mounting problems in securing adequate numbers of qualified personnel who are essential to the treatment and rehabilitation of mental patients, in addition to the problems of providing adequate facilities for treatment and rehabilitation programs.

RELATIONSHIP OF PUBLIC MENTAL HOSPITALS TO COMMUNITY SERVICES

The public mental institutions for the mentally ill or mentally retarded are only one element, albeit an important one, in the spectrum of services available to the mentally disturbed in the community. The more flexible and dynamic the hospital program, the more easily and fully can it coordinate its services with those that can be rendered by the community program before, during, and after a patient's hospital stay. Sound professional judgment would indicate that the greater the integration of the hospital into the broad-based program for the comprehensive care, treatment, and rehabilitation of the mentally ill the better the patient will be served.

A basic observation is the heartening progress reported for the last 7 years relative to reduction of the resident patient population in hospitals. This trend must and can be extended and accelerated if new and presently available procedures and practices are energetically undertaken—and if all levels of government (Federal, State, and local), together with the private citizenry in the com-

munity, face up to their responsibilities in this area. If this is done, it is the considered opinion of many professionals that within the next 25 years it is possible for the mental hospital as it is now known to disappear from the scene. Following the medical tradition of bringing services to the patient rather than the patient to the service, there will develop within the community more appropriate service facilities of various types which can deal more effectively with the problems of the mentally ill individual. The community mental health center is the prototype of such facilities.

Until community-centered mental health services are more widely developed, there is an imperative need for improving the quality of care in existing public mental hospitals. The mental health project grant (under authority of title V) offers an ideal mechanism for stimulating and encouraging the State hospitals to strengthen their therapeutic programs through the undertaking of demonstration projects. Active treatment-oriented programs, particularly those interwoven with an active prevention and treatment-oriented program in the community, are especially desirable and provide an excellent transitional device to bridge the gap between the present State hospital and the emerging community mental health programs.

THE HOSPITAL IMPROVEMENT PROJECT GRANT

In the light of the foregoing considerations and, based on the conviction that the large mental hospital as it presently exists is anachronistic and cannot serve the mentally ill in optimal fashion, it is believed that the most appropriate support which can be given to the State mental hospitals at the present time is the encouragement of demonstrations of improved methods of care, treatment, and rehabilitation. The great need is to demonstrate in each State mental hospital successfully demonstrated ways and means of mobilizing all available resources to move patients out of hospitals.

The President's budget for 1964 contains a request for \$12 million to provide for the first phase of a three-phase program to upgrade the quality of care in State institutions for the mentally ill and for the mentally retarded.

This would make possible the awarding of grants to up to one-third of the State institutions for the mentally ill and the mentally retarded, at amounts of up to \$100,000. (In 1965 and 1966, funds will be requested to permit funding of projects in the other two-thirds of the institutions.) In the first year of the program the Institute will, through technical assistance and staff consultation, stimulate and encourage the development of high-quality projects in each State. As the purpose of this program is to upgrade the quality of care of the mentally ill in this country, it is believed that concern with geographical distribution is not only appropriate but in the best interests of the mentally ill and mentally retarded throughout the country. These projects, as required by law for all mental health project grants, must be reviewed by the National Advisory Mental Health Council and recommended favorably as a basis for support.

On humanitarian grounds alone, our Nation can ill afford the continued loss of human resources represented by vast numbers of persons with mental and emotional problems. The time has come for affirmative action on a massive front—from programs aimed at the prevention of mental illness to those which would affect the cure and rehabilitation of the mentally ill, and their return to productive community life.

In view of available knowledge, developing techniques, and experience gained in other nations, among other considerations, it is incumbent upon the Nation to take such steps as may be required to improve preventive programs and care for the mentally ill and the mentally retarded to a level on a par with the best that is available throughout the world. The proposed program for hospital improvement projects represents an essential component of the President's program to achieve that goal.

SPECIAL REPORT ON PROJECT GRANT PROGRAM

Mr. FOGARTY. We will also place in the record the special report on the entire project grant program.

(The report referred to follows:)

The mental health project grants program was established by title V of the Health Amendments Act of 1956 (Public Law 911) (section 303 of Public Health

Service Act) which authorized the Surgeon General "to make grants to State or local agencies, laboratories, and other public or nonprofit agencies and institutions, and to individuals for investigations, experiments, demonstrations, studies, and research projects with respect to the development of improved methods of diagnosing mental illness, and of care, treatment, and rehabilitation of the mentally ill, including grants to State agencies responsible for administration of State institutions for care, or care and treatment, of mentally ill persons for developing and establishing improved methods of operation and administration of such institutions."

Institutional projects deal with administrative and operational procedures, new methods and concepts of treating patients, and integration of the institution with the community.

Community projects relate to modes of prevention and early detection of mental illness; more effective and more economic alternatives to conventional hospitalization; rehabilitation and reintegration of discharged patients into the life of the community; encouraging interest and sound understanding of mental health in the community; and better utilization of community agencies presently dealing with these problems.

Many projects concern such special mental health problems as aging, alcoholism, delinquency, drug addiction, mental retardation, and school mental health.

The goals of this program are to develop and disseminate new knowledge and encourage the use of what is already known, with particular emphasis on projects and programs which coordinate existing resources and which move toward a comprehensive continuum of prevention, care, treatment, and rehabilitation. In addition, the program seeks to encourage State and local governments, foundations, and research agencies to provide support for similar activities.

During the first 5 years of this program, 412 projects were supported in the total amount of \$25,310,000. The following table shows an annual summary:

Mental health project grants awarded, fiscal 1958-62

	1958		1959		1960		1961		1962	
	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount	Num- ber	Amount
New projects.....	65	\$1,903,354	47	\$1,149,771	62	\$1,377,056	121	\$2,635,239	117	\$4,192,254
Continuations and supplements.....	3	8,440	55	1,731,696	90	2,760,574	117	3,634,971	131	5,916,705
Total.....	68	1,911,794	102	2,881,467	152	4,137,630	238	6,270,210	248	10,108,959

AGING

The mental health project grants program has made 10 grants for projects related to mental health of the aged. One grant was made for a survey of institutions and agencies in a Georgia community to determine the possibilities for developing coordinated services for the aged. A grant was made to the San Antonio, Tex., Housing Authority, to explore ways of improving the administration of a program for the elderly, to investigate new design features in housing, and to define methods for making the aged an integral part of the community's social structure.

A small grant was awarded to support a study which provided a description of members of a senior citizens' day center in terms of certain psychological and social history variables and to relate these variables to levels of participation in the center's activities. One of the concerns emanating from this latter study centered about the realization that the program appeared to attract those individuals who were already functioning effectively and did not reach the older person who was functioning less effectively. Another grant to the same senior citizens center is for a project which seeks to train older persons, through a curriculum of class and field work, to serve specific community activities. This is being accomplished with the cooperation of the State department of mental health, a medical school, and two universities.

A State mental hospital project in California was related to the question of whether it was necessary for elderly patients to remain in the specialized

setting of a State psychiatric hospital when such care was no longer indicated. The findings indicated that the increasing number of patients 65 years of age and over in California State psychiatric hospitals resulted, in part, from the continued long-term care of patients in the 40- to 64-year-old bracket so that they became part of the geriatric patient population. It was found that approximately 50 percent of the patients studied could be adequately cared for in a non-psychiatric setting providing adequate supervision, nursing, and medical services. Another project in a State mental hospital setting centered about devising, planning, and designing a type of community nursing facility for the care of a group of geriatric patients being admitted to State hospitals.

The primary objective of a project in Massachusetts was to develop ways and means of sustaining the geriatric patient extramurally and to minimize the admission of the nonpsychiatric geriatric patient to State mental hospitals. Analysis of early data showed that the majority of the aged admissions were psychotic, and factors such as economic need, physical illness, and social isolation played a relatively minor role in hospitalization.

A vocational service agency in Illinois has established a workshop for older persons in order to demonstrate the beneficial effects on the aged when they participate in a productive work atmosphere. This project proposes to demonstrate that a productive work situation will retard, arrest, or reverse the negative aspects of psychological aging.

A grant was made to a home for the aged in New York City to support a study to determine what measurable effects occur when a workshop program which closely simulates a genuine work situation is introduced into the institutional setting.

ALCOHOLISM

Nineteen grants have been made for studies and programs related to alcoholism. A project at Massachusetts General Hospital is studying the effectiveness of treatment and rehabilitation beginning with the alcoholic's admission to the emergency ward. Washington University in St. Louis is demonstrating a treatment program which includes both inpatient and community services. The Ohio Department of Health has received a grant to assist in establishing alcoholism treatment centers in several communities. The Family Service of Cincinnati is developing a casework service for families of alcoholics. Mississippi has a grant for demonstration of an alcohol education program.

COMPREHENSIVE COMMUNITY MENTAL HEALTH PROGRAMS

An ideal community mental health program should include a diagnostic and evaluation service, an emergency clinic, an inpatient facility, rehabilitation and aftercare facilities and services, foster home care for adults and children, mental health information and education services, and consultation resources for community agencies and organizations.

Most of the projects in the early years of the mental health projects grant program focused on various individual facilities, services, and techniques which may be appropriate parts of comprehensive communitywide programs. Such projects have been conducted in mental hospitals, general hospitals, medical schools, child centers, universities and colleges, public and private schools, public health departments, and family and other community agencies.

More recently, an increasing number of projects have been concerned with the development of comprehensive community programs. Thus a grant was recently made to a large suburban county health department in Maryland to assist in the demonstration of a program for the comprehensive community care of the mentally ill. Other grants have been made to county and city governments in California for the development and evaluation of local mental health programs. Rhode Island received a grant to assist research development in the State mental health program, and Minnesota has a grant for evaluating its State mental health program.

In addition, Nebraska, New Mexico, and Wyoming have projects developing and demonstrating community mental health services.

Recent trends indicate that there will, in the future, be a sharp increase in the number of project grants awarded for developing and demonstrating comprehensive mental health programs.

JUVENILE DELINQUENCY AND CRIMINALITY

About 60 projects related to juvenile delinquency and/or criminality are being supported by the mental health project grants program. Many of these center around (1) the causes and prevention of delinquency; (2) community programs for the prevention and control of delinquency; and (3) mental health programs in prisons and correctional institutions.

A major demonstration program to attack the problem of juvenile delinquency on the lower east side of Manhattan is being partially supported by project grant funds. Comprehensive in its scope, the program administered through the Mobilization of Youth, Inc., has two objectives: (1) to provide expanding opportunities to the youth of the project area, and (2) to arrest self-defeating modes of behavior that prevent the young people from exploiting these opportunities. NIMH-supported activities will be primarily directed toward the second objective, and will be concerned with providing specialized services to individuals and families, and to groups.

Considerable grant support for training in mental health concepts and techniques is being given juvenile court judges, police officers, youth workers, educators, and institutional personnel. Among these training efforts, the institutes for juvenile judges and police officers sponsored by the University of Minnesota, and the National Council of Juvenile Court Judges are of particular importance.

Other project grants are concerned with the following:

An interstate approach to problems of juvenile delinquency;

Special delinquency problems—the mentally defective delinquent, youth gangs, multiproblem families, and alcoholic and narcotic offenders; and

Community services for the unwed pregnant adolescent.

The first report of the information clearinghouse of the National Council on Crime and Delinquency, supported by project grant funds, was issued this past year and briefly describes about 700 current projects related to crime and delinquency.

MANPOWER

The mental health project grants program has made about 100 grants to assist inservice training programs, staff development programs, and mental health personnel recruitment programs. The range of these grants is great, covering many different types of personnel, and providing training in a number of mental health problem areas. Examples of the types of training programs supported by mental health project grant funds are listed as follows:

Fourteen States have received grants to enable State mental health directors and hospital superintendents to attend the institute for psychiatric administrators at the University of Chicago. The continuation and expansion of this program, which has recently moved to the University of Wisconsin, is being assisted by grant funds.

The Western Interstate Commission for Higher Education and the Southern Regional Education Board have grants for assisting inservice training of personnel in mental hospitals and institutions for the mentally retarded.

The University of Minnesota is conducting highly successful summer institutes for juvenile court judges and juvenile police officers, and the National Council of Juvenile Court Judges has received grants for the development and support of training institutes for juvenile court judges.

Both the National Association of Social Workers and the Council on Social Work Education have received grants for social work personnel development.

Several grants have been made to universities and public school departments for projects related to training and developing school mental health personnel.

Other inservice training programs include the clergy, nurses, volunteer workers, and mental health agency administrators.

MENTAL HOSPITAL PROGRAMS

In the first 5 years of the mental health project grants program, 100 grants were made to mental hospitals or mental hospital-related programs in 37 States. Additional States benefited from two grants to the Southern Regional Educational Board and two to the Western Interstate Commission for Higher Education for institutional staff development and inservice training programs.

Among the problems being studied through grants awarded to institutions are :

The extension of mental hospital services to the community and cooperation between the mental hospital and community agencies ;

The unique county mental hospital system in Wisconsin ;

The development of better systems and techniques for collecting, recording, analyzing and utilizing medical data :

The treatment of adolescents in adult psychiatric wards ; and

Family centered treatment of schizophrenia.

Twenty-three grants were for small amounts for staff travel and consultation in connection with the designing and developing of projects and programs. An additional 20 grants were for the in-service training and personnel development of hospital superintendents, research personnel, nurses, social workers, business administrators, aids, and volunteers.

Considerable increased interest and activity in hospital improvement programs has been exhibited recently, and it is expected that in the future the number of hospitals designing and developing projects for possible inclusion in the mental health project grants program will be greatly increased.

MENTAL RETARDATION

Thirty-three grants have been made to institutions for the mentally retarded, medical schools, hospitals, and community agencies for the development and demonstration of new and improved techniques for care, treatment, and rehabilitation of the mentally retarded.

A major grant to the University of Nebraska College of Medicine assisted in the development of a preadmission, receiving, diagnostic, and treatment center. Reports from this center indicate that interdisciplinary investigations are very important in making a correct diagnosis, and that a significant number of retarded children can be adequately cared for without institutionalization.

Another major grant, to the Pacific State Hospital in California, is assisting the development of a medical data processing laboratory which will make possible new techniques to identify, define, and quantify the significant variables relative to diagnosis and treatment of the mentally ill.

Other studies in medical settings include a project at the University of Oklahoma Medical School on collaborative management of mental retardation research and services, and a project at Children's Hospital in Los Angeles to study phenylketonuria in school-age retarded children.

Both the Western Interstate Commission for Higher Education and the Southern Regional Education Board have grants to assist State institutions in staff development through in-service training. In addition, community agencies in New York and Wisconsin have grants to assist in demonstrating programs helping retarded youth in developing occupational and self-care skills.

NARCOTICS

Eight grants have been made for projects related to narcotics. In New York City a study is being made of heroin use by adolescents. The Institute for the Study of Crime and Delinquency in California has a grant for a halfway house for narcotic offenders. The University of California has received grant funds to support a scientific conference on narcotics problems. A narcotics addiction service center is being established in Stamford, Conn.

SCHIZOPHRENIA

About one-third of the projects supported by the mental health project grants program are related, in some way and in some degree, to treatment and rehabilitation of schizophrenics. Some of these are described briefly as follows:

Projects in Massachusetts, New York, and Illinois are exploring and developing day nursery, day hospital, and educational programs for schizophrenic children.

Family-centered treatment in schizophrenia is being demonstrated in North Carolina, Pennsylvania, and California.

In New York City, a Columbia University project is studying the effects of a continuous comprehensive treatment program for schizophrenia.

In Massachusetts a study is being made of role relations and rehabilitation of married male schizophrenics after hospitalization.

In Kansas a study is being made of the feasibility of a treatment program for chronic schizophrenics in which the aid-patient relationship is the primary treatment instrument of the hospital team.

A Kansas State Hospital team has explored and evaluated comparatively three different treatment methods for chronic schizophrenia, with particular study of a method derived from current prevailing concepts of the psychopathology of schizophrenia and mental hospital functioning.

SCHOOL MENTAL HEALTH

The mental health project grants program has made 58 grants related to school mental health. These projects included: demonstrations and studies in the use of behavioral science research in the education and rehabilitation of emotionally disturbed children and adolescents; types of interventions and preschool programs that might help culturally deprived and mentally retarded children to be more successful in school; effective methods of deploying and utilizing mental health personnel in schools; the relationship of school learning to psychotherapy and parent counseling; the relationship of psychotherapy and parent counseling to school learning; the collaboration and content of the various professional groups offering pupil personnel services to schools; and the development of a master research program in the content of pupil personnel services.

One of the major problem areas in school mental health is the emotionally disturbed child and his family. Such children are usually found in residential schools or special programs in public schools. One project by a University of Michigan team will investigate the similar and dissimilar ways in which various schools in the United States provide educational services to these children and their parents. A project at George Peabody College for Teachers at Nashville, Tenn., which is now in its second year, is trying to train and use a new professional discipline, adapted from successful French and Canadian programs, to work with emotionally disturbed children in residential settings. In this program two new residential programs have been developed, one in Tennessee and one in North Carolina.

In St. Louis and New York there are continuing studies on early identification of children who are developing mental health problems in school. The South Carolina Mental Health Commission is initiating studies on prevention through preschool mental health checkups and appropriate interventions.

Projects related to the education of culturally deprived children include one in which an attempt will be made to develop processes for the socialization and education of Indian children in boarding schools. Another is concerned with the impact of different types of educational approaches on Indian personality. The New York Institute on Developmental Studies has a long term study of ways of helping underprivileged children to be better prepared for school through enriched nursery school programs. Other projects on the use of behavioral science research in helping culturally deprived children learn are under way in Quincy, Ill.; Murfreesboro, Tenn.; and Stockton, Calif.

Several projects are investigating the special educational needs of retarded children.

A 5-year project has been initiated to bring the services of pupil personnel, noninstructional services into closer alliance and support with the total school effort. In this project a number of organizations representing personnel who offer such services joined together to form an Interprofessional Research Commission on Pupil Personnel Services. These organizations include the American Medical Association, the American Psychological Association, the American Nurses Association, the National Association of Social Workers, the American Speech and Hearing Association, the Council of Chief State School Officers, the National Association of Secondary School Principals, the American Personnel and Guidance Association, and others. This commission will initiate and develop demonstration programs in methods of effective collaboration and coordination of pupil personnel services with school programs and out-of-school resources and will carry out and stimulate research on preventive mental health programs in schools. In addition, major study will be devoted to discovering how the mental health professions can provide behavioral science information for more effective use by teachers, principals, parents and children.

The application of new knowledge to schools and to the children they serve can have a highly significant potential impact on mental and emotional illnesses. At the present time there are approximately 41 million children and youth enrolled in schools and by 1965 this will rise to 55 million. Further grants will be made to find ways of helping handicapped as well as normal children and adolescents be more intellectually and emotionally effective as learners and citizens.

CATEGORICAL CLINICAL RESEARCH CENTERS

Mr. FOGARTY. Why are you cutting back the categorical clinical research centers from \$2 million to \$1,750,000?

Dr. FELIX. Well, we cannot go everywhere at once. We have set up and are supporting six of these centers now.

At the present time, we would like to get these shaken down before we move forward.

Now, the difference between this year's budget and next year's, is due to the fact that there was, in the first year of establishment of those centers some additional expenditures for equipment and other initial items which will not be recurring—they will be nonrecurring items.

CONTROL GRANTS TO STATES

Mr. FOGARTY. I notice the control grants are broken down between grants-in-aid, and planning.

Would you explain what is done under each?

Dr. FELIX. Yes, sir.

The control grants, which are in the amount of \$6,750,000 are the grants which have traditionally been made to States on allocation by formula which is described in section 314(c) of the Public Health Service Act.

These are grants designed to assist the States in their central office, in the development of extramural aspects of the programs. There is no increase requested over the previous year.

PLANNING GRANTS TO STATES

The other part of these funds is \$4,200,000 which is a request for a second and final year of an item contained in this year's appropriation, at the same amount, \$4,200,000, which are funds which will be allocated to the States according to formula, to allow them to plan, to develop long-range, community based plans for comprehensive mental health programs.

These grants would be made on a 50-50 matching basis; no State to receive less than \$50,000 for each of the 2 years.

They will be required to consult with all agencies in the State, public and private, at the local as well as the State level in order to involve the agencies which have a role to play, or which could be developed into playing a role in a community based mental health program.

These plans then will be the basis for further action by the States, with the full knowledge that, as the programs grow and develop in the States, the States probably will change or modify plans as needed to keep up with changes. I hope they will move more rapidly than our best estimates would let us know at the present time.

Mr. FOGARTY. We will place your special report on planning grants in the record.

(The report follows:)

SPECIAL REPORT: PLANNING GRANTS TO THE STATES

In its action on the 1963 appropriation for the National Institute of Mental Health the Congress provided \$4.2 million to be used to assist the States in the development of plans for comprehensive mental health programs. These mental health planning grants provided the basis for a totally new grant-in-aid undertaking by the Institute, an undertaking quite similar to the highly successful Hill-Burton authorization for planning grants for the development of State plans for medical and hospital facilities. They have been allocated under the provisions of section 314(c), Public Health Service Act, and will provide each State with a grant of at least \$50,000. (See table attached.)

The Institute has viewed the provision of these funds as a challenge both to the Federal Government and to the States and communities; it has, therefore, devoted considerable time and effort in the planning for their most effective use. Because this is a new program, the Institute in its apportionment plan has programed these funds for availability in the third quarter of 1963, in order that the Institute might have sufficient time to develop the necessary guidelines and criteria for the States in applying for these funds.

At his meeting with the State and Territorial mental health authorities on January 9, 1963, the Surgeon General formally announced the availability of these funds to the States upon the submission and approval of their plans. Since that time, the Institute has sent out guidelines to the States and hopes that all States will have submitted approvable applications by June 30. Although it has not been possible to make these funds available to the States earlier in the year, it will be possible for the States to carry over these funds for utilization in the next succeeding year. In addition, as a part of the President's proposed national mental health program, an additional \$4.2 million for planning grants is requested in 1964. This will make a total of \$8.4 million available to the States to assist in the planning of statewide mental health programs. It has been felt that this planning grant-in-aid support is necessary in order to assist the States to develop truly comprehensive mental health plans.

In making these funds available to the States, the Federal Government will provide timely and necessary support and further stimulus to statewide movements already underway as a result of the final report of the Joint Commission on Mental Illness and Health.

The following is a brief statement covering the issues which the Institute has spelled out in its guidelines to the States. To be truly comprehensive in their planning, the States must include concern with such diverse areas as facilities and services, research and training, legislation and financing, and many other matters. Further, in developing its plans, each State must work with its communities toward programs which have their roots in those communities. Such community based mental health programs should provide a broad spectrum of mental health services emphasizing a continuum of care, should assure coordination among all relevant community resources, and should work toward the prevention of mental illness, and for promotion of mental health. To encompass a complex problem of this magnitude, support for planning as a clearly defined activity, is necessary.

The goals of the mental health planning funds program are to provide:

1. Guidelines and support for a comprehensive statewide planning operation leading to the development and strengthening of community based programs; and
2. Guidelines and criteria for assessing the adequacy of a comprehensive plan.

The State plans should develop priorities for short- and long-range State goals, and should outline and document the need for new and expanded programs. The planning may also suggest some different uses of currently appropriated State, local, and Federal funds. It is reasonable to expect that there will be increased funds for mental health programs in the future from various sources. However, planning activities are viewed as necessary and valuable without reference to specific increases.

DEFINITION

Planning may be defined as the process by which a State or community orders the steps toward explicit goals. This process includes development and use of means for gathering data as to needs, the integration and analysis of such data, the selection of goals, priorities and methods, and the allocation of available resources to achieve the selected goals.

The Institute will, in general, evaluate the submitted planning proposals against this operational definition, with full recognition of individual differences in the mental health programs and needs in the States. A State planning proposal which contains the elements described above may be expected to lead to the development of a comprehensive plan.

GATHERING INFORMATION

States have varied greatly in their ability to gather and use information effectively. Strengthening information gathering would, therefore, be a valid and necessary component of planning.

The States undoubtedly need to obtain current and accurate information on patients and families, general population characteristics, service resources (hospitals, clinics, schools, etc.), health manpower (both mental health and allied professions), research programs and resources, training programs and resources. Information gathering which is otherwise sufficient may need strengthening in relation to the mental health components of chronic disease, aging, mental retardation, alcoholism, drug addiction, delinquency, and school programs.

The planning proposal should indicate clearly not only how such information will be secured for immediate use in the development of a comprehensive plan, but also should concern itself with the means and mechanisms which will be used to incorporate such data collection systematically and permanently. The addition of staff to strengthen this area may have high priority in a State's use of planning funds.

INTEGRATION AND COORDINATING INFORMATION

The planning grant encourages integrated and coordinated use of collected information. Effective information gathering requires a pooling of facts and effort by a diversity of agencies with kindred interests. The information thus gathered must be easily available to all groups participating in the planning. States can use the planning funds to sponsor meetings of those groups, both to plan coordinated data-collection activities, and to discuss the meaning of the data. The States can also use planning funds to provide professional and technical assistance in the methods of information gathering. Coordination and integration of information is important for the development of the comprehensive plan, and for the long-range implementation of the plan and its subsequent modification to reflect changing needs.

THE SELECTION OF GOALS, PRIORITIES, AND METHODS

The general goals selected by the State will reflect its broad long-range objectives in mobilizing its total resources for prevention, screening, diagnosis, treatment, rehabilitation, consultation, research, training, health, education, and health promotion, as parts of a statewide comprehensive program of mental health. These goals must be reached by intermediate steps which are based on present knowledge and resources, and which change with circumstances and new knowledge.

To plan these steps, explicit attention must be paid to the administrative arrangements, interagency cooperation, legislation, budgeting facilities and equipment, personnel, analysis and dissemination of professional and technical information, training, and research that will be required. Provision should be made for the continuous program evaluation and replanning required to meet changes as these develop.

The planning proposal should describe the means and mechanism that the agency given responsibility for mental health planning will use in order to insure the active and continuing participation of all relevant State and community agencies and groups in this planning and decisionmaking process. The

proposal should indicate the means that will be employed to effect a balance in the use of State and local resources so as to foster local initiative and participation. Planning funds may be used to defray the costs of these activities.

TO PROPOSE ALLOCATION AND DISTRIBUTION OF AVAILABLE RESOURCES

All of the steps described above lead to decisions about the allocation and distribution of resources. Because time, personnel, and funds are always limited, it is important that priorities be set. A statewide approach to the gathering of information and agreement as to how efforts are to be coordinated will strengthen the position of the planning group as it proposes courses of action. If this is to achieve coordination among a variety of agencies and groups, both private and public, the planning will need to be firmly based on the needs of all the people, rather than just those that are the responsibility of a particular agency.

In all States, several agencies have direct mental health concerns and interests, and other agencies and groups, public and private, are less directly, but no less importantly involved. The document submitted by the States, therefore, should reflect an approach toward planning for the entire State rather than for the program of any one mental health agency in the State. The proposed planning should consider the mental health needs of all people in all parts of the State. Such planning should take into account the people who are living at home in the community, those living in public and private hospitals and institutions, and those mentally ill not receiving any professional attention. It should also consider the mental health needs of schoolchildren, of welfare clients, and of people under the jurisdiction of correction agencies. The range of services to be considered should certainly include prevention, screening, diagnosis, treatment, rehabilitation, consultation, research, training, and health education. No one State will be able at once to give full and equal attention to all dimensions of a comprehensive program, but the full range of possibilities should be studied even in making choices and setting priorities. It follows that, in addition to all the key State health and mental health agencies, including mental health associations and medical and other professional societies, being involved in the planning process, a number of other groups including education, welfare, corrections, and health facilities construction agencies need to be associated.

A basic component of the planning process is the assessment of problems, resources, and needs, and the evaluation of current activities. The planning proposals submitted by the State must include a description of its intended assessment and evaluative activities. For example, consideration should be given to methods of ascertaining the numbers and location of mentally disabled people in the State, as well as the location, adequacy, and types of services and facilities available to the mentally disabled. The plan and budget submitted should clearly indicate the relationship of specific activities to the establishment of the central process of planning.

There are differences among the States in the nature and extent of their mental health problems, in the development of their resources, in their history, in their size, and in their administrative arrangements. While the overall goals may be similar in all States, the methods of approach, the priorities, the new ideas, will vary from State to State. It is therefore most important that the planning proposal be as specific and detailed as possible. It should include not only a description of planning goals, but also an outline of the intended administrative and technical procedures. Adequate staff is important in order to strengthen planning activities. The planning proposal should indicate the provisions for such staffing.

Planning funds are designed to strengthen planning activities and thereby develop a comprehensive plan for mental health services in each State. Planning will highlight the need for new services.

Support for such services will come, as it comes now, from local, State, Federal, and private sources.

The mental health planning funds have been described with some indication of the scope of statewide planning envisioned in this program. In order to qualify for these funds, States will submit proposals which describe their intended planning activities—activities designed to meet the mental health needs of all of the people. Such planning will require the broadest possible participation within each State. The planning group will be responsible for an overall State plan.

It is believed that the provision of these planning funds by the Federal Government can form the basis for the development by the State of truly comprehensive mental health programs, with particular emphasis on and attention to those at the community level.

Allocations for mental health planning grants

State	1963	Estimate, 1964	State	1963	Estimate, 1964
Alabama.....	\$69,900	\$69,900	Nevada.....	\$50,000	\$50,000
Alaska.....	50,000	50,000	New Hampshire.....	50,000	50,000
Arizona.....	50,000	50,000	New Jersey.....	103,700	102,500
Arkansas.....	50,000	50,000	New Mexico.....	50,000	50,000
California.....	271,400	277,100	New York.....	280,700	282,400
Colorado.....	50,000	50,000	North Carolina.....	95,400	96,000
Connecticut.....	50,000	50,000	North Dakota.....	50,000	50,000
Delaware.....	50,000	50,000	Ohio.....	171,000	173,300
District of Columbia.....	50,000	50,000	Oklahoma.....	50,000	50,000
Florida.....	96,400	99,800	Oregon.....	50,000	50,000
Georgia.....	81,100	82,000	Pennsylvania.....	201,100	197,500
Hawaii.....	50,000	50,000	Rhode Island.....	50,000	50,000
Idaho.....	50,000	50,000	South Carolina.....	52,700	52,300
Illinois.....	171,000	167,200	South Dakota.....	50,000	50,000
Indiana.....	84,100	83,200	Tennessee.....	74,500	73,700
Iowa.....	51,300	50,100	Texas.....	182,200	185,600
Kansas.....	50,000	50,000	Utah.....	50,000	50,000
Kentucky.....	63,100	62,200	Vermont.....	50,000	50,000
Louisiana.....	66,200	65,700	Virginia.....	77,500	78,500
Maine.....	50,000	50,000	Washington.....	50,800	51,800
Maryland.....	55,100	54,300	West Virginia.....	50,000	50,000
Massachusetts.....	88,900	86,400	Wisconsin.....	72,100	72,400
Michigan.....	137,800	137,600	Wyoming.....	50,000	50,000
Minnesota.....	63,600	62,400	Guam.....	50,000	50,000
Mississippi.....	52,800	52,400	Puerto Rico.....	57,300	57,300
Missouri.....	78,300	76,400	Virgin Islands.....	50,000	50,000
Montana.....	50,000	50,000			
Nebraska.....	50,000	50,000	Total.....	4,200,000	4,200,000

PSYCHOPHARMACOLOGY

Mr. FOGARTY. What have you been doing in the area of psychopharmacology?

Dr. FELIX. I have mentioned two of the rather interesting developments this morning when I spoke about the drug which can be injected, now, into the fatty depots in the body, and has a long-range effect.

One injection will last about 2 weeks, and they now have developed a drug which is specifically effective in paranoid-schizophrenia.

Our program this year in psychopharmacology, in the fiscal year 1964, is at a level of about \$17,720,000. This program, as you know, is concerned primarily with the early testing of drugs after they have been developed; first in animals, later early clinical testing, and finally testing these drugs on large populations to find out what their specific effects are on specific kinds of mental illnesses.

Mr. FOGARTY. Well, are you continuing at the same rate or are you stepping up this program or are you cutting back or what?

Dr. FELIX. Our 1964 estimate is about \$3 million—a little over \$3 million—over our 1963 program. We are at the present time in the process of, or have just finished, testing over 100 drugs in this psychoactive series. We have 15 hospitals in the country cooperating with us at the present time, in common design, so that data are comparable back and forth between the testing.

Mr. FOGARTY. We will place your special report in the record.
(The report follows:)

SPECIAL REPORT: PSYCHOPHARMACOLOGY SERVICE CENTER PROGRAM
INTRODUCTION

The psychopharmacology program of the National Institute of Mental Health has, as its major objectives, the scientific assessment of the clinical assets and reliabilities of existing psychoactive drugs, and the continuing assessment of new psychoactive drugs. Further, the program encompasses the study of the basic mechanisms of action of these agents, the development of improved methods for the study of drug effects and the provision of special services, to investigators in psychopharmacology.

During the past year, two major clinical collaborative studies were completed, and methodological issues basic to understanding and assessing drug effects have been clarified considerably. Although no new important psychoactive drugs have emerged in the last 12 months, the special grant program supporting the evaluation of new drugs is functioning effectively, and programing related to the metabolism of drugs and to the testing of new compounds has also been developing well.

CURRENT CLINICAL RESEARCH

New drugs

The search for new types of psychoactive drugs has not been dramatically productive. However, one new series of tranquilizers, the phenylpiperazines, which act similarly to chlorpromazine, has been developed by the Sterling-Winthrop Research Institute. A grant-supported study, now in press, reports that one of these, oxypertine, is equal in potency to the phenothiazines now on the market; and it has no more serious side effects.

This adds a fourth class of drugs to the existing antipsychotic chemicals. Of these, the phenothiazines are well established, while the efficacy of the Rauwolfia alkaloids is generally agreed to be of a lower order. The third group, consisting of haloperidol and related chemical compounds, is controversial. Haloperidol is widely and enthusiastically used in France, Belgium, Germany, Italy, and Russia. However, one National Institute of Mental Health grantee at Manhattan State Hospital has reported consistently poor results with this drug in the same type of schizophrenic patient that apparently responds well to the drug in Europe. Now collaborating with a Belgian psychiatrist, the grantee will attempt to determine the reasons for this differential response to the same drug by similar patients on two continents.

Another grantee, at Stanford University, found on early clinical tests that haloperidol was relatively ineffective in newly hospitalized schizophrenics. However, when he collaborated with other investigators in four Veterans' Administration hospitals in a controlled, grant-supported study to compare haloperidol with thiopropazate, a standard phenothiazine, the two drugs were found to be equally efficacious in newly admitted schizophrenic patients, and produced about the same incidence of neurological side effects.

Almost all other studies have indicated that haloperidol is less effective than the phenothiazines in American patients, but is more likely than the phenothiazines to produce severe neurological side effects. American investigators have suggested that one reason for the popularity of the drug in Europe may be the widely held belief of European psychiatrists that extrapyramidal side effects must be produced in schizophrenic patients to achieve effective tranquilization.

Similarly, grantees and other investigators have explored compounds chemically related to chlordiazepoxide, and have failed to reveal, to date, any compounds with unusual clinical properties.

One intriguing development in new drugs has come from the attachment of a fatty acid to fluphenazine, a highly effective phenothiazine, to make a fatty acid ester. When administered by injection, this ester exerts a pharmacologic effect for 2 weeks or more. Early work on this compound by a grantee at Baylor University suggests that injection may be a safe and effective way of treating patients who cannot be relied upon to take oral medications.

Combination of drugs and resistance to drugs

Two major and interrelated issues in clinical psychopharmacology have come to the fore during the past year. The first is the use of combined drugs in the

treatment of psychiatric patients. This issue has been clearly presented in a grant-supported study at Hillside Hospital in Glen Oaks, N.Y. The investigators reported that many schizophrenic patients and a few depressed patients showed considerable relief of such symptoms as anxiety, tension, delusions, and hallucinations when they received phenothiazine derivatives. At the same time, however, this type of patient became apathetic, so that he could not be judged to be really improved. When these investigators added imipramine, an antidepressant, to the phenothiazine derivative, the patient's interest in his environment and his general effectiveness as a human being were substantially increased. Since, as reported by a grant-supported investigator at the University of Michigan, among others, imipramine by itself will often intensify the psychopathology of schizophrenic patients, the possibility is raised that a suitable level of phenothiazine medication, combined with an antidepressant, may achieve a favorable clinical response in patients who would have responded inadequately to either medication alone.

The therapeutic efficacy of a similar combination of drugs—trifluoperazine, a phenothiazine, and an amino oxidase inhibitor—is being studied intensively by the early clinical drug evaluation unit at the University of Minnesota.

Finally, grantees at St. Louis State Hospital report that chlordiazepoxide, a mild tranquilizer usually used in neurotics, caused remarkable improvement in a group of long-term chronic schizophrenic patients when it was superimposed on their original maintenance medication of phenothiazines.

The issue of combining drugs and shifting from one drug to another becomes of primary importance when one considers the large number of chronic patients in our public psychiatric hospitals 10 years after the advent of phenothiazine derivatives. Are these patients completely resistant to drugs? Are there, in fact, patients who would improve enough to be discharged if shifted to a different drug or given a combination of drugs? Are there patients who have improved on drug therapy but who need nonpharmacologic treatment or the special efforts of social workers before they can find a place in the community? And are there other patients who are not taking their drugs, or whose bodies are metabolizing the drugs so atypically as to make the drugs ineffective? Would these patients do better were they to receive a combination of agents? This entire problem deserves special attention in the coming years.

Psychotomimetic agents

Psychotomimetic agents, such as LSD (lysergic acid diethylamide) and psilocybin, have been used for 15 years as pharmacologic tools in the study of human psychological functioning. When these compounds are administered to normal volunteers in an experimental setting, the individual usually experiences some anxiety accompanied by distorted visual experiences, some feelings of loss of contact with reality or depersonalization, and, rarely, true hallucinations or paranoid ideas, plus a moderate number of mild physical side effects.

In the last year, an increasing number of published reports depict a quite different use of these agents. For example, these drugs have been given to subjects who were led to expect that they would have quite unusual experiences which would teach them a great deal about themselves and their personalities. They were further led to expect this experience to be therapeutic. With these expectations, the subjects apparently reported the experience to be not unpleasant, informative about themselves and their relations to other people, and, on occasion, intensely mystical, resembling religious conversion. Artists taking these drugs apparently often claim to feel that they are made "more creative."

Much of the reported unusual therapeutic properties of these drugs is open to serious question as these agents have been given to unstable individuals, principally subjects with severe character disorders of psychopathic personalities, and usually by therapists who have had extensive and intense experiences with the drug themselves, and were thus highly biased in favor of these agents. Some professional groups including the Southern California Psychiatric Society, have expressed concern over the possible misuse of these agents.

It is certainly clear that these drugs produce quite different and much more profound effects when given in a therapeutic setting as against an experimental one. Whether these effects are attributable primarily to the drug or to the setting is in question. Whether the long-term effects of such agents administered as therapy are predominantly good or predominantly bad remains to be seen. Several instances of prolonged psychotic states in users of these drugs have been

reported, and there have been informal case reports of the illicit abuse of these agents to achieve unusual states of consciousness. Since these drugs lose their effects when taken continuously, they cannot be said to be addicting in the sense that heroin is. Nevertheless, there is apparently some psychic dependency on these drugs and some illicit traffic in LSD. This situation may be partially corrected by Sandoz Pharmaceutical Co.'s recent decision to stop distributing these drugs for clinical investigation, except under very special conditions.

The outstanding positive aspect of these agents lies in their reported efficacy in the treatment of chronic alcoholism and other severe personality disorders which have been almost totally unresponsive to other drug treatments, or, for that matter, to other forms of psychiatric treatment.

There is, therefore, a need to develop sound clinical studies that will test both the effectiveness and adverse effects of these agents, but recognition must also be given to the existence of a new class of agent which may be misused by sociopaths and other individuals with unstable personalities.

Early clinical drug evaluation program

This year, 3 new early clinical evaluation units were added to the previously existing 13, and the capacity of 1 of the earlier units was doubled by increased financial support. One of the new units will give special attention to the evaluation in outpatients of interesting drugs already established as safe in inpatients. Another unit will pay special attention to the use of drugs in the treatment of geriatric psychiatric patients. Applications have been solicited and are being reviewed from units concentrating on evaluating safe drugs in the treatment of psychiatric disorders of childhood and in geriatric patients with organic brain damage.

The number of drugs under study in these units increased from 44 last year to 66 by the end of this year.

The twice-yearly meetings of the early clinical drug investigators have become increasingly productive. This has come about through the informal comparison of results obtained from drugs studied jointly by several of the investigators and by the increasing attention given to improving the methods by which new agents may best be studied.

In May 1962, a meeting was held between representatives of evaluation units and the subcommittee on psychotherapeutic drugs, medical director's committee of the Pharmaceutical Manufacturers Association, to discuss mutual problems. In general, relations among the staff of the Psychopharmacology Service Center, the principal investigators in the units, and the drug companies involved in this work appear to be quite good. The effects of the Drug Amendment of 1962 and the new regulations published by the FDA on the Psychopharmacology Service Center's program in general and on the early clinical drug evaluation program in particular are difficult to predict. To date, it would appear that their anticipation of the new regulations has led drug companies to increase rather than decrease the number of compounds being submitted to grant-supported investigators for possible study.

Drugs in schizophrenia—Acute schizophrenia

The first nine-hospital collaborative study of drug effectiveness in newly admitted acute schizophrenic patients has now been completed. A total of 350 patients was studied during a 6-week period of controlled drug therapy at 9 hospitals selected to represent the major types of facilities treating acute schizophrenics in this country. Three are well staffed private or university hospitals, two are city hospitals, and four are State hospitals.

The patients were randomly assigned to chlorpromazine, the standard and oldest effective phenothiazine derivative; fluphenazine, a relatively new phenothiazine distinguished by its very low effective dose (1 milligram equals approximately 100 milligrams of chlorpromazine) and its alleged relatively high incidence of neurological side effects; thioridazine, a new phenothiazine allegedly causing a very low incidence of neurological side effects; and an inert placebo.

Although all relevant analyses of the data collected from this study have not been made, it is clear that the three drugs in all the hospitals were greatly superior to placebo in the treatment of schizophrenia. Such diverse symptoms as apathy, auditory hallucinations, hostility, paranoid delusions, incoherent speech, and hebephrenic giggling responded well, while the social behavior and self-care of patients, as observed by nurses, improved. In general, the data support the hypothesis that these drugs are broadly efficacious against all major types of schizophrenic symptoms rather than only affecting specific symptoms of

excitement and agitation. None of the three drugs emerged as distinctly superior to the others. Although the neurological side effects showed the expected trends, with fluphenazine causing the most and thioridazine the least, the differences were less striking than one would have expected from published reports. Fluphenazine, indeed, caused fewer total side effects than did the other two drugs.

Factors that can predict favorable responses to individual drugs or to the drugs as a group are now being sought in an analysis that should be completed in the next few months.

A series of smaller collaborative studies of more recent drugs for schizophrenia has been made in four Veterans' Administration hospitals, under a grant to Stanford University. A psychologist at Kansas State University, supported through a research career development award, has also collaborated in these studies. This group has derived from a simple clinical rating scale a typological approach to schizophrenia. In this approach, the majority of schizophrenics newly admitted to these hospitals can be classified either as "paranoid schizophrenics," as "core schizophrenics" (a composite of undifferentiated schizophrenics, catatonic schizophrenics, and hebephrenics), or as "depressed schizophrenics" on the basis of their rating scores.

In a small controlled study, the investigators report that no difference could be found between perphenazine, an older phenothiazine, and acetophenazine, a new derivative, when results on all schizophrenic patients given each drug were compared. However, when the results for the paranoid and core schizophrenics were considered separately, acetophenazine was superior to perphenazine in paranoid schizophrenia and inferior to it in core schizophrenia. Classifying these patients by clinical diagnosis alone did not reveal this difference. It may well be that pictures of syndromes developed from detailed ratings of psychopathology are more precise and more useful than are diagnoses per se.

This is almost the only study in a large and growing clinical literature to show a clear qualitative difference between two generally effective phenothiazines. For this reason, the typologic approach as well as the interesting new drug, acetophenazine, are being incorporated into the second phase of the larger multihospital study described above. Other new features of this second study will be a longer period of controlled medication, and some new measures of clinical change.

Drugs in schizophrenia—chronic schizophrenia

A grant-supported study carried out at Napa State Hospital in California, comparing chlorpromazine, trifluorpromazine, perphenazine, and prochlorperazine with placebo in chronic schizophrenic patients hospitalized for 2 to 10 years, has been completed. The investigators report that all drugs are significantly more effective than placebo in reducing clinical symptoms. Of the drug-treated patients, 24 percent were able to return to the community, whereas only 4 percent of the placebo-treated patients were able to do so. The usual rate of release for patients with this duration of schizophrenia was between 1 percent and 3 percent in the California State hospitals prior to the introduction of drugs. This study also failed to reveal significant differences in efficacy among the active drugs, although chlorpromazine was reported to have significantly more adverse side effects than perphenazine or trifluorpromazine.

A grant-supported study at the University of Minnesota compared a newer phenothiazine, carphenazine, with an older one, thioridazine, using a new statistical approach: sequential analysis. This method assigns each member of successive pairs of patients to each drug, and analyses the outcome for each pair, as they finish the planned period of treatment. In this manner, a significant difference between two treatments may be detected earlier and with a smaller number of patients than would be the case if a larger number of patients were assigned to each drug and analysis of the results was delayed until all had completed the treatment. In this particular study, unfortunately, the drugs proved to be so similar that no increased efficiency resulted. Nevertheless, this methodological advance may be valuable in future studies in which the drugs being compared differ more substantially in clinical efficacy.

Drugs in depression

Investigators at the Westchester division of the New York Hospital have reported on a grant-supported, controlled study which showed that two antidepressive drugs, deanol and a combination of meprobamate and benactyzine were no more effective than placebo in treating hospitalized depressed patients.

A multihospital study of patients admitted to Massachusetts State hospitals is continuing to investigate the comparative effectiveness of placebo, electroconvulsive therapy, imipramine, and two monoamine oxidase inhibitors (phenelzine and isocarboxazid) in depressed patients. This study, which initially did not include a placebo-treated group, had shown earlier that electroconvulsive therapy was superior to isocarboxazid; imipramine and phenelzine showed intermediate efficacy. Recently, in a report of the analysis of a larger body of data, the placebo-treated patients were shown to have improved significantly more than patients treated with isocarboxazid, although less well than patients receiving the other treatments. This underlines the continuing need for placebo-treated control groups in clinical drug evaluations of depressed patients.

Grant-supported investigators at Rutgers University, studying drug treatment of depression in New Jersey State hospitals, have reported imipramine to be slightly superior to electroconvulsive therapy in depressed patients. On the other hand, a grant-supported controlled study of imipramine carried out at Springfield State Hospital in Maryland failed to demonstrate the superiority of imipramine over placebo in a small group of depressed patients. There was, however, a trend favoring the use of this drug in patients with severe psychotic depressions. This trend was not apparent in patients with neurotic depressions or with prominent depressive symptoms as part of a schizophrenic illness.

Some of the relatively inconsistent results with imipramine in various studies may be due to differences in types of patients involved in these studies. A grant-supported project at Hillside Hospital in New York has paid close attention to the type of patients responding to imipramine. In this study of 180 patients falling into a variety of diagnostic categories, patients with hopeless, self-deprecatory depression in the context of the perfectionistic pre-illness personality showed clear elevation of mood, improved behavior, and greater interest in their environment. A similar group of patients, but with a greater tendency to deny or to minimize their problems, blaming their condition on outside events, showed a drug response characterized by excessive and somewhat unrealistic denial of all problems. A smaller group of patients with little depression, but with chronic episodic attacks of anxiety and with fears of being left helpless if exposed to ordinary stresses, were surprisingly benefited by imipramine. Another group, composed of withdrawn, preoccupied, and suspicious patients with schizophrenia, showed striking agitation and disorganization on the drug. Other patients, also diagnosed as schizophrenic, but with less severe disorganization and more anxious depression, tension, and inertia, showed markedly improved social functioning. Forty patients, mostly with fixed symptoms of many years duration, showed no behavioral effects from imipramine at all. Although patients with depressive diagnoses in general were helped more by the drug than were those with schizophrenia, still, half of the schizophrenics improved with imipramine therapy.

These observations serve to underline the extent to which variability in clinical drug response occurs even within groups of patients with similar diagnoses. More specific determinants of drug response must be taken into account if results of clinical drug studies are to become more meaningful.

Drugs in neuroses

The grant-supported, special collaborative study of drugs in neurotic outpatients carried out in Pennsylvania and Maryland has completed its initial study comparing meprobamate with placebo in anxious neurotics. It has reaffirmed the superiority of meprobamate in the treatment of anxiety symptoms. In one of the three clinics it has demonstrated that psychiatrists who are enthusiastic and therapeutically positive obtain greater differences between meprobamate and placebo than those psychiatrists who are reserved or neutral. Differences among the three clinics with regard to the attitudes of the patients toward their doctors may account for the failure of the other two clinics to show a differential effect in the psychiatrists' approach.

A grant-supported, double-blind controlled study at the University of Pennsylvania has also shown meprobamate to be generally superior to phenobarbital and to placebo in neurotic outpatients.

A study comparing a combination of d-amphetamine and barbiturate, a preparation widely used in medical practice, with d-amphetamine alone and with a barbiturate alone has been completed by a group of collaborating British general practitioners. The combination did not prove to be superior to d-amphetamine in the treatment of mild depressions or to barbiturate for anxiety states.

Drugs in children with psychiatric disorders

Grantees at the University of Nebraska report chlorpromazine to have statistically significant, but rather minimal, effects on a small group of children hospitalized for a variety of emotional disorders. In general, the effects were inhibiting or depressing in nature. Another grantee at New York University reports another phenothiazine, trifluoperazine, to have positive therapeutic effect in young schizophrenic children. Although these effects fall short of truly dramatic improvement, the beneficial changes are noteworthy because this type of illness is singularly resistant to all other known therapies.

Investigators at the Johns Hopkins University have reported d-amphetamine to have a beneficial effect on the behavior of disturbed, institutionalized, adolescent delinquents, confirming uncontrolled reports of the tranquilizing effects of this stimulant drug in younger individuals suffering from behavior disorders. Because perphenazine, a tranquilizer effective in adult psychotics and neurotics, had failed to show superiority to placebo in this same setting in an earlier study, this more recent work serves to underline the differences in drug response likely to exist between children and adults.

BASIC RESEARCH

Studies in patients and normal subjects

Drugs, in addition to their therapeutic potential, are also useful as research tools for the study of psychiatric conditions. In particular, barbiturates, both sodium amytal and sodium pentothal, have been administered intravenously at a constant rate and the dosage at which the subject showed signs of sedation has been determined by measuring changes in the EEG, by noting the point at which speech became slurred, or by noting the point at which the subject actually fell asleep. These approaches have been most actively studied by a group of investigators under grant support at the University of Iowa. They report that patients diagnosed as having psychotic depressive reactions, that is depressions of considerable severity, show a remarkably reduced threshold for sedation as compared with normal subjects, while patients with neurotic depressive reactions, milder depressions with a more obvious anxiety component, show elevated sedation thresholds. A grant-supported study at the University of North Carolina has recently revealed that the psychogalvanic skin response, a measure of the electrical conductivity of the skin, is also sensitive to the intravenous injection of a barbiturate. The threshold for the obliteration of this response shows a similar and statistically significant discrimination between the psychotic depressive reactions and psychoneurotic depressive reactions; the psychotic depressions showing much lower thresholds.

A similar type of measure has been explored by the group at the University of Iowa noted above, namely, the evoked cerebral potential. Highly specialized equipment has enabled them to both detect and measure, by averaging the number of responses, the magnitude of the brain wave response to a mildly painful stimulation of a nerve in the wrist. If two such sensations are transmitted one after the other, the EEG response to the second sensation is markedly reduced. The time necessary for the brain to "recover" and show a second response to painful stimulation of as great magnitude as the first response is called the recovery time.

Patients with psychotic depressions show markedly slowed recovery time as compared with normal subjects. It is interesting to note that although imipramine decreases recovery time in normal volunteer subjects producing a response resembling that of psychotic depression itself, patients with psychotic depression who improve on imipramine show a return of the recovery time to essentially normal values.

The above studies indicate a generalized reduction in the reactivity of the nervous system to outside stimuli in patients with severe psychotic depressions.

Two grantees at the Johns Hopkins University have published an excellent review on the enhancement of human performance by caffeine and the amphetamines. They conclude that d-amphetamine in particular has been reliably shown to improve performance of a variety of types in the presence of fatigue or boredom. However, some experiments, particularly those by a grant-supported group at the Massachusetts General Hospital have shown the drug to be more effective than placebo in improving the performance of college athletes carrying out such brief acts as shotputting and weight throwing, where fatigue and boredom could hardly be considered significant factors. They

also note that the enhancement of performance produced by the amphetamines in particular is accompanied by seemingly little in the way of side-effects either during the period of action of the drug or subsequent thereto.

There is an increasing body of evidence that indicates that effects of drugs are influenced substantially by the expectations of the subject. Further, a subject's expectations appear to be potentiated when he feels the physiologic effects of a drug are present. In controlled studies of drug effects in normal subjects, it would appear that the subject who expects a certain type of drug action, but who receives a placebo, often does not respond to suggestions given at the beginning of the experiment. But, those who receive active drugs and feel some physiological effect, often interpret these effects in terms of the suggestions given at the beginning of the experiment, even if those expectations are different from the subjective events that usually occur when the drugs are given. It has also been shown that the social situation may act in the same manner to influence the subjective response to drugs. A grantee at Columbia University reports that subjects given epinephrine can be induced to feel either anger or euphoria according to the social situation occurring during the period of drug activity.

Animal studies

Special grants have been awarded during the past year to the University of Pittsburgh and Indiana University to establish behavioral pharmacology laboratories. Personnel at these laboratories, in collaboration with the staff of the Psychopharmacology Service Center, will develop new techniques and standardize older ones for assessing the effects of drugs on animal behavior. In addition, a contract is being negotiated with a commercial testing laboratory to evaluate new compounds, synthesized and submitted by NIMH grantees for biological testing. This systematic program for perfecting and utilizing animal screening tests for detecting psychotropic activity in new chemical compounds will reduce the danger of overlooking potentially extremely valuable new drugs synthesized by grantees because of inadequate or unavailable biological testing of compounds.

Reviews of the scientific literature on two important determinants of animal behavior were published last year by grantees. A review of over 400 articles concerning drug action on the brain-stem reticular formation was prepared at Stanford University. The author points out that present techniques in neuropharmacology do not allow us clearly to conclude that specific effects on the reticular formation of the brain represent the major mechanism of action of certain classes of compounds. It would appear, however, that the anesthetic agents and amphetamine definitely affect this area, that certain other classes of compounds have ambiguous or nonspecific effects, and yet others, such as convulsants, hallucinogens and interneuronal depressants probably have no effect on the reticular formation.

The other review deals with positive conditioned reinforcement or the techniques by which a previously neutral stimulus becomes rewarding through association with a positive reinforcer. The authors, who now are staff members of Harvard Medical School and the University of Maryland, find that recent experiments have revealed several techniques for the development of effective conditioned reinforcers, and that these techniques provide powerful means for controlling behavior.

It is widely recognized that the effective dose of a given psychotropic drug will vary many-fold from one patient to another. Similar results are obtained with laboratory animals. Several investigators are attempting to determine what factors are involved in producing those large interindividual differences. A grantee at Southeastern Louisiana College found that some rats readily become addicted to morphine and others do not. Wondering whether this was an inheritable trait, he mated addiction-prone females with equally addiction-prone males, and likewise paired addiction-resistant rats. In each case the offspring resembled their parents in addiction-liability, thus suggesting a genetic factor in addiction to narcotics. At Boston University School of Medicine, two new strains of mice have been developed by selective breeding, one of which is more and the other less sensitive to pentobarbital than is the original strain from which they were developed. Sensitivity was tested by observing whether the mice could cling to an inclined screen after receiving doses of the barbiturate. These experiments suggest that responsiveness to specific drugs is determined, at least in part, by inheritable characteristics.

Investigators at Baylor University have found that chlorpromazine will retard the disappearance of the naturally occurring polypeptide, bradykinin, when incubated in vitro with powdered dog brain. Morphine, reserpine, and LSD lack this protective effect. These grantees postulate that bradykinin may play a role in the tranquilizing action of chlorpromazine.

At the University of Pittsburgh, grantees have made aqueous extracts of kava root, which is used by natives of Oceania to make an intoxicating beverage. These extracts were administered to laboratory animals and their behavioral and neurophysiological effects were studied. Fractions were isolated that reduced hyperemotionality and impaired avoidance responses in rats. Muscular relaxation and a slowing of cerebral electrical activity occurred in cats, and a reduction in the spontaneous activity of mice was observed. Work is continuing to further isolate and characterize these naturally occurring substances that possess tranquilizer-like properties.

Drug metabolism

The Psychopharmacology Service Center has had a continuing interest in the metabolism of psychoactive drugs, in particular the clinically potent phenothiazine derivatives. There is a strong possibility that differences in clinical response to these drugs, including the complete drug resistance observed in some chronic schizophrenic patients, may be explained by individual differences in the way these drugs are handled by the body. Work carried out under research grants and within the pharmaceutical industry has made it clear that the metabolites of chlorpromazine and other phenothiazines formed in human subjects differ strikingly from those formed by various experimental animals. For this reason definitive work must be done in human subjects. The problem is complicated by the fact that these drugs may be chemically modified in the gastrointestinal tract as well as in the body tissues. The exposure of these drugs to the gastrointestinal tract may be much greater than assumed and the opportunity for chemical modification thereby increased; a grantee at UCLA has reported that these drugs are continually being reexcreted into the intestine in the bile and reabsorbed again into the blood.

To speed the development of appropriately sensitive and quantitative methods for measuring the levels of phenothiazines and their metabolites in the blood and urine of patients, contracts were negotiated with the Battelle Memorial Institute, the Southwest Research Institute and Monsanto Research Corp. in the spring of 1962. This work has been proceeding well. Using gas chromatography, amounts of drug or drug metabolites, weighing as little as a billionth of a gram, can be detected in human urine. There is every reason to believe that this method will be applied to clinical research in the coming year. Gas chromatography will be used in the second phase of the nine-hospital study of phenothiazines in acute schizophrenics, noted previously, to see whether patterns of drug metabolism are in fact related to the degree of clinical improvement produced by the drug.

Chemical synthesis and pharmacological testing

Grant and contract-supported work on the synthesis of compounds of interest in psychopharmacology has been handicapped for several years by the inadequacy of the pharmacological testing facilities usually available to medicinal chemists. For this reason a contract is being negotiated for pharmacological testing of selected compounds synthesized under the psychopharmacology program. Such services should become available in the spring of 1963. It will be particularly important to have metabolites of active phenothiazines and other psychoactive drugs studied to see whether any of the metabolites are more active than the parent drug. Among new compounds being developed by grantees, a substituted pyridindole, synthesized by grantees at Harvard Medical School, is of particular interest since the preliminary animal testing available to these investigators showed that the new compound potentiates both the sedative effects of barbiturates and alcohol and the stimulatory effects of amphetamine. The compound appears to potentiate these drugs in a manner quite different from that observed with monoamine oxidase inhibitors or chlorpromazine. Grantees and consultants in medicinal chemistry have been most enthusiastic about the potential of this special pharmacological testing service.

SCIENTIFIC INFORMATION ACTIVITIES

The Scientific Information Unit of the Psychopharmacology Service Center now encompasses some 19,000 reprints, manuscripts, monographs, books, and

other materials relevant to psychopharmacology. This material is coded in such a way that retrieval of specific information is relatively easy. The use of Flexo-writer punched tabs to print out bibliographic references greatly facilitates the preparation of reference lists. During the past year approximately 2,500 requests for information from investigators working in psychopharmacology were handled. Two thousand of these could be answered quite simply, using readily available material. Approximately 500 required more detailed and extensive searches. The efficiency of the present operation is attested to by the fact that the majority of even the more detailed searches were carried out and replies transmitted to the investigator within a single day following receipt of the inquiry. Searches almost never took longer than a week.

The staff of the Psychopharmacology Service Center and of the National Clearinghouse for Mental Health are collaborating in providing the Food and Drug Administration with rapid up-to-date information on side effects and toxic effects reported for psychoactive drugs. This material will be obtained from the continuing flow of papers and manuscripts collected by the Center.

The Scientific Information Unit staff participated in the preparation of a highly detailed depth indexed bibliography covering the effects of drugs on the electroencephalogram. This is being published in a supplement to an electroencephalographic journal. Detailed annotated bibliographies have been prepared under grant support covering all published controlled studies of insulin shock therapy and Metrazol shock therapy. The first of these has been published and the second is now being printed.

Translations for all Russian language articles in the files of the Scientific Information Unit have been completed, covering the period between 1958 and the present. About 150 articles have been done. Major reviews on serotonin, on the monoamine oxidase inhibitors and on the placebo effect have been translated from French and German. Some 150 other articles have been translated from a variety of languages, mainly covering reports of side effects due to psychoactive drugs. Information concerning the availability of these translations is disseminated through the journal, *Technical Translations*, published by the Department of Commerce.

Five issues of the Psychopharmacology Service Center Bulletin, a newsletter designed to provide informal rapid communication of all kinds of information to psychopharmacologists, were published in 1962. The March issue contained a detailed compendium of information concerning the psychoactive drugs available at that time for prescription use. This issue has been extremely popular; it has been used as a teaching aid, both by medical schools and by psychiatric residency programs.

Psychopharmacology Abstracts, a new abstract journal in psychopharmacology, begun in 1961 is being continued in 1962. It has been received with great enthusiasm by the physicians and other investigators on the Unit's mailing list.

The activities of the Scientific Information Unit of the Psychopharmacology Service Center are being administratively transferred to the National Clearinghouse for Mental Health Information. The staff of the Psychopharmacology Service Center will continue to participate actively in the scientific aspects of this important documental activity.

DIAGNOSTIC RESEARCH

Mr. FOGARTY. All right. What about Diagnostic Research. Do you wish to say anything more on that?

Dr. FELIX. I have reported this morning about the study of the new diagnostic test used which can identify, with considerable accuracy, schizophrenic patients.

There has been work done by several investigators in the area of so-called sociopaths or psychopaths—a group of University of Michigan at Ann Arbor, Dr. Lippit and his group have been working with some of the problems of identifying characteristics of juvenile delinquency and other types of psychopaths. There have been developed through our own scientists at the National Institute of Mental Health a series of new and improved rating scales for identifying both intelligence level and some other—some personality deviations in children.

Dr. Nancy Bailey has been working for over 25 years on this.

These, I would say, are the principal areas with which we have been working the diagnostic field.

RESEARCH WITH ST. ELIZABETHS HOSPITAL

Mr. FOGARTY. Tell us about your St. Elizabeths project?

Dr. FELIX. We have, as you know, one building at St. Elizabeths—the William A. White Building—in which we are carrying out several different kinds of research. There are laboratories in the building for basic studies in problems of physiology, biochemistry, and so forth. There are a number of very interesting studies being carried on ward management, and the treatment of patients in ward situations.

Dr. Joel Elkes, formerly of Birmingham University in England, is the head of that. He has as the clinical director Dr. Fritz Freyhan, who was formerly at the State hospital in Delaware—a most excellent physician.

One interesting development, one that is interesting to me at least, and delights me: They have been making home visits in the District of Columbia area following up patients discharged from this unit.

At first there was some question on the part of some of the doctors, as to whether this would be worth while or not. They say now that both they and the patients have benefited by this. They, in that they know a great deal more about the patient than they have ever known, seeing him just in the hospital. The patient has had immediate treatment as situations arose.

They make home visits just like the family doctor makes them. They are following up the patients after discharge.

It was through this laboratory that there was developed the finding that the intact human body can metabolize substances which will produce psychotic symptoms, and this is now being followed up. Now that we know that the body can metabolize such substances, even if the result was a substance which is not usually found, we know that this is possible, and this now being followed up from the point of view of what toxic byproducts there may be in the body which may produce the symptoms one sees in schizophrenic and other conditions.

AGING

Mr. FOGARTY. What are you doing in the field of aging?

Dr. FELIX. Aging is really a joint job of several of the Institutes and other departments of the Public Health Service so ours is one brick in the building, not the total story.

Mr. FOGARTY. In other words, you are not doing much.

Dr. FELIX. Well, we are doing quite a bit of research but we are not doing a lot of fieldwork as we have in these other areas.

Mr. FOGARTY. You say on page 148:

Of special note are the studies in aging being conducted as part of the expanding institute international research grant program. One tripartite study will permit cross-national comparisons of aging—in the United States, England, and Denmark.

Dr. FELIX. This is a study between three countries, as to what factors in the various countries seem to be responsible for failure

to adjust to society. The studies are biological, social, psychological in nature, all three, and through these, we hope to be able to establish some new techniques with regard to the care and rehabilitation of elderly people.

I am of the strong opinion that in a high percent of the cases there is no need for aging people to be put in mental hospitals. In most cases, they will not become confused, and develop symptoms which are objectionable—if the proper social and emotional supports are maintained for them in their declining years. I think the work going on in Denmark and in one or two places in England are particularly pertinent here.

In England, for instance, in one of the places we wish to study, is a home for the aged, or a community, rather, not a home, a community for the aged in York, where these people have to take care of themselves; cook their own meals; wash their own clothes. It looks almost cold-blooded on the face of it, but they find that as long as they can keep these people active and carrying on with their routine functions which they carried on all their lives, they stay intact much better.

This year, incidentally, in fiscal 1963, we are spending over \$2¾ million in this field, and next year this will be over \$3¾ million.

LETTER FROM PRESIDENT, AMERICAN PSYCHIATRIC ASSOCIATION

Mr. FOGARTY. I have a letter addressed to me signed by Dr. C. H. Hardin Branch, president of the American Psychiatric Association, going on record in favor of this program of planning grants to States. I will put that in the record.

Dr. FELIX. Thank you.

(The letter mentioned above is as follows:)

AMERICAN PSYCHIATRIC ASSOCIATION,
Washington, D.C., February 18, 1963.

HON. JOHN E. FOGARTY,
Chairman, Subcommittee for the Department of Labor and Health, Education, and Welfare, House Office Building, Washington, D.C.

DEAR CONGRESSMAN FOGARTY: It is my pleasure as president of the American Psychiatric Association to express the great satisfaction experienced by our organization and its governing council on the action taken by the 87th Congress through the appropriation act for the Department of Health, Education, and Welfare, which became law on August 14, 1962.

We feel that this appropriation of additional mental health grant-in-aid funds to support comprehensive mental health planning in the States and territories is of the utmost importance as an initial step in the implementation of action for improved methods of prevention of mental illness, the provision of adequate mental health services, and the promotion of mental health in the Nation.

We further feel that the action taken by Congress through the Mental Health Study Act of 1955, as well as this last act of August 14, 1962, evidences recognition of the need to further our knowledge in the field of mental health and provide improved mental health services in the Nation.

It is our sincere hope and belief that, as a result of proper planning activities in mental health in the States and territories, will come action, which will be of positive benefit to the population as a whole in this problem of national concern.

We further hope that Congress and the national administration will continue offering the States and territories, their assistance in the form of grant-in-aid funds and consultative services to further develop action programs.

I am pleased to express our congratulations to you, to the members of your subcommittee and to the Members of the House of Representatives for having taken this initial step necessary for the implementation of the recommendations of the Joint Commission on Mental Illness and Health.

The membership and governing council of the American Psychiatric Association, cognizant of its own responsibility in the improvement of the health and welfare of the Nation, stands ready to offer our most enthusiastic support and assistance to Congress and the national administration in the performance of the task ahead, in facing this No. 1 health problem of this Nation.

Sincerely yours,

C. H. HARDIN BRANCH, M.D.,
President.

LETTER FROM AMERICAN ACADEMY OF CHILD PSYCHIATRY

Mr. FOGARTY. I also have a letter from the American Academy of Child Psychiatry, signed by Joseph Weinreb, M.D., secretary. They adopted some resolutions. We will put that in the record, and if you care to comment on their suggestions, you may, after you have had a chance. You can do it for the record.

Dr. FELIX. All right.

(The letter is as follows:)

AMERICAN ACADEMY OF CHILD PSYCHIATRY,
February 13, 1963.

Hon. JOHN E. FOGARTY,
Chairman, House Office Building,
Washington, D.C.

MY DEAR CONGRESSMAN: As secretary of the American Academy of Child Psychiatry I have the honor of transmitting to you the accompanying resolutions which were passed by the academy in January 1963.

The American Academy of Child Psychiatry is an association of physicians who combine special training and long experience in the field of dedication to the remedying of the emotional disorders of children. These resolutions express our concern and our offer to do our part in improving and preserving the health of the youth of our country.

Sincerely yours,

JOSEPH WEINREB, M.D., *Secretary.*

Resolved, That the American Academy of Child Psychiatry gives highest priority to the manpower problem in child psychiatry; that we will participate with other appropriate professional groups to establish mechanisms for the study, promotion, and strengthening of recruitment and training efforts in the field.

In consideration of implementing this resolution, we—

- (1) Declare the manpower problem a matter of first priority.
- (2) Encourage the establishment and staffing of a National Commission of Psychiatric Manpower.
- (3) Identify and assign responsibility to appropriate committees to give priority to manpower problems over the next several years.
- (4) Express our willingness to work in collaboration with the Council on Mental Health of the American Medical Association looking to the establishment of a counterpart commission on mental health manpower by the American Medical Association.
- (5) Express our interest in participation in organizing a coordinating council at the national level for planning purposes in the mental health manpower field.
- (6) Urge regional groups of the academy to organize similar coordinating councils on a regional basis, and encourage the regional groups to work actively in behalf of training and recruitment at the county and community level with particular reference to capitalizing on the county medical society as a resource.
- (7) Participate in organizational mechanisms which will bring into play the thinking and efforts of professors of psychiatry, chiefs of professional training, and other leaders in institutional and university training centers and render their mutual assistance more effective.

Resolved, That the American Academy of Child Psychiatry recognizes that shortages of physicians, psychiatrists, and particularly child psychiatrists, and new needs for broadening the scope of medical practice and its specialties, calls

for major attention to the pools of college-trained persons from which medical schools draw their applicants, and the schools in which medical students and medical graduates are trained with respect to their number, location, and the quality of their product.

To this end the American Academy of Child Psychiatry calls the attention of its members to the efforts of the American Association of Medical Colleges in support of Federal aid to medical education and encourages support of the American Association of Medical Colleges in these efforts.

Specifically, this includes support of the concept of—

(A) Matching funds by the Federal Government for modernization and expansion of existing schools, and construction of new schools.

(B) Financial aid to students of medical schools in nonrefundable scholarships.

(C) General support of medical education including various levels of graduate training.

(D) Coordination of all Federal grants relating to the field of medicine and continuation of use of non-Federal consultants.

And further, That the American Academy of Child Psychiatry would be interested in participating in the study of new methods of financing medical education.

And further, That methods be developed to encourage selected college and high school students to prepare for careers in the mental health professions.

Finally, That the American Academy of Child Psychiatry bring to the attention of the governments of the various States the importance of increasing facilities for undergraduate and postgraduate medical educational facilities.

ARTICLE FROM PROVIDENCE JOURNAL

Mr. FOGARTY. In Monday's Providence Journal, my hometown paper, there is an article by Selig Greenberg, who has had a great deal of experience in writing for this paper over the years, especially in the field of medicine. It is entitled "Psychiatric Revolution; Organized Medicine Backs a New Idea on Treating the Mental Illness Patients." It has your picture and your name is prominently mentioned. I am going to put this in the record.

(The newspaper article follows:)

PSYCHIATRIC REVOLUTION

ORGANIZED MEDICINE BACKS A NEW IDEA ON TREATING THE MENTAL ILLNESS PATIENTS

(By Selig Greenberg, Journal-Bulletin staff reporter)

Lost in the shuffle of the day's news was a recent item of the man-bites-dog variety from Chicago; the American Medical Association has come out in favor of one of the programs proposed by President Kennedy in the health field.

The President's proposal, now backed by the AMA, calls for Federal grants to the States to help finance the construction and initial operating costs of a broad network of community centers for the prevention, diagnosis, and treatment of mental illness.

The objective of the far-reaching plan, submitted by Mr. Kennedy in a special message to Congress last month, is to reverse the traditional approach of isolating the mentally ill in big institutions and to center treatment instead in the local communities with the goal of preventing prolonged hospitalization and returning patients as rapidly as possible to a useful role in society.

The idea has received high praise at a conference of representatives of State medical societies and mental health agencies called by the AMA's Council on Mental Health. The administration program was said to be generally in line with recommendations approved last summer by the AMA board of trustees and house of delegates.

CROWDED INSTITUTIONS

Aside from the novelty of an AMA endorsement of one of Mr. Kennedy's health plans, it is encouraging to find the organized medical profession among the backers of a new concept of tackling the enormous problem of mental illness.

The State and Federal Governments, and to a lesser degree, some of the local governments, now are spending two and a half billion dollars a year on the treatment of the mentally ill. Most of this money is used to maintain about 600,000 patients in large State mental hospitals. Many of these institutions are antiquated, overcrowded, and understaffed and few of them provide more than custodial care for the great majority of their patients.

Leading psychiatric authorities contend that the most humane and economical answer to the problem of mental illness lies in the provision of a broad array of medical and social services, ranging from the prevention and early detection of mental disease through posthospital care, within easy reach of every community.

Many experts argue that the outlook for recovery is most promising when the mentally ill are not isolated but are treated within the context of home, friends, school, and work. They also feel that the treatment of mental illness should be integrated as much as possible within the setting of the general hospital.

This view received authoritative backing in 1961 in the voluminous report of the Joint Commission on Mental Illness and Health after a 5-year study conducted under the leadership of the American Psychiatric Association and the AMA.

The Commission urged the expenditure of "vastly increased sums of money" and substantial Federal grants for more adequate care and treatment of mental patients.

It recommended that no further State hospitals with a capacity of more than 1,000 beds be built, that all existing State hospitals with more than 1,000 patients be gradually converted into centers for the long-term care of the chronically ill, and that smaller institutions be developed for the intensive treatment of those with good prospects for improvement or recovery.

It also called for the establishment of psychiatric units for short-term hospitalization in all general hospitals of 100 or more beds and of fully staffed mental health clinics for outpatient treatment of the emotionally disturbed for each 50,000 of population.

Rhode Island, whose only State mental hospital has about 3,400 patients, is one of the few States which have made at least a modest beginning in the direction of encouraging local mental health clinics to provide early treatment for those needing help and in reducing the number of those requiring hospitalization.

Under a law passed last year, the State will match local funds on a 50-50 basis for approved psychiatric clinics. Such aid is limited in any one fiscal year to 50 cents per capita in the area to be served. Warwick and East Providence are now in the process of organizing such programs and will become eligible for State aid upon approval expected soon from the State director of social welfare.

A SHIFT IN FOCUS

The tranquilizers, stimulants, hypnotics and a wide variety of other drugs and such new hospital techniques as group therapy and day care and night care have revolutionized the treatment of mental illness. They have infused new hope into an area long enshrouded in fatalism and hopelessness. They urgently demand a shift of focus from the back wards of our big mental hospitals, where thousands are doomed to vegetate for the rest of their lives, to smaller institutions for intensive care and to community-centered outpatient clinics.

"Since medieval times the idea has been to segregate the mentally ill," Dr. Hamilton C. Ford, chairman of the AMA's Council on Mental Health, has said. "Perhaps this was all that could be done at a time when the average stay in an institution was 30 years. It is no longer true today, when a period of weeks is often all that is required. We now know that institutional care can sometimes be more of a detriment than a help."

"In view of what we have learned in recent years," Dr. Robert H. Felix, Director of the National Institute of Mental Health, stated recently, "the concept of a large mental hospital as the most desirable place for a sick mind seems rather ridiculous. There is no valid reason why mental illness cannot be treated like any other illness—in a doctor's office or a local hospital if necessary."

Since each of us "lives in a neighborhood," Dr. Felix asserted, the best thing to do when we get sick is to keep us as close as possible to our natural setting.

"When a person needs help," he said, "that is not the time to wrench him from his family, his friends, all that is familiar to him, and deliver him to an institution. The first thing he has to do in an institution is to get readjusted, and this can impose a severe jolt, particularly when he has been thrown among

hundreds of other sick people and he has the feeling that he has been sent away, that being out of sight often also means out of mind.

LIKE RUNNING AWAY

"What the mental patient needs as much as drugs and professional techniques is a good therapeutic environment. And since the patient must go back to his own community when he gets out, it is best for him to be treated right there. Otherwise, he may come to the conclusion that the only thing to do is to run away. Going to an institution is, in a sense, running away."

Not only does the traditional isolation of the mental hospital breed public apathy, Dr. Felix commented, but the patient very often gets "lost" there.

"The involved mechanisms needed to run a big institution often prevent an individual from getting the personalized care he needs so desperately," he declared. "It might take months to get him into the proper line of treatment, and these are the early months so crucial to his recovery. In contrast, the principal objective of the proposed new program is to make seeking help for mental illness as simple and uncomplicated as getting medical attention for a 'tummy' ache."

This, admittedly, is a goal still some time off in the future. But many authorities are convinced that family physicians can play a key role in resolving many emotional and mental problems and in providing at least the initial treatment when more specialized psychiatric attention is required.

"There is no reason," Dr. Felix said, "why any physician can't treat mental illness just as well as any other common ailment. No one is in a better position to spot early signs of emotional disturbance than the family doctor. He sees it often enough in his normal work by handling many patients with symptoms but no apparent organic causes of disease. And when the same man who has treated a patient for other ailments in the past treats him for a mental disorder, the patient comes to realize that there is nothing bizarre about mental illness. This can go a long way toward removing the stigma so long associated with it."

Latest thinking also is that psychiatric treatment is fully feasible in general hospitals when hospitalization is required. The local outpatient clinic may frequently provide a substitute for hospitalization, and it can certainly serve a vital function in posthospital care.

No matter what the course of treatment, the aim is to interrupt the patient's day-to-day life as little as possible. In some cases hospitalized patients may even continue to work, the only difference being that they would leave for the office from the hospital and return there at night.

Bringing psychiatric treatment into the general hospital need not necessarily involve any large-scale expansion of such hospital beds. In fact, expert opinion is that the overall bed-space needs of psychiatry can probably be reduced, for with good care many mental illnesses can be treated better out of the hospital than in it.

UNLOCKING THE WARDS

Studies at a number of institutions have demonstrated this. A group of psychotics treated as outpatients at a New York hospital were away from their jobs only 6 weeks. A similar group which was institutionalized spent 6 months at the hospital. Another study at a California hospital showed that even severely ill schizophrenic patients could, after a period of hospitalization, be cared for out of the hospital with as little as half an hour of individual psychotherapy once a month.

"In the past few years," Dr. Felix said, "it has been demonstrated time and again in a number of mental hospitals that when you unlock wards and give patients some personalized care and progressively greater responsibility, there is a remarkable increase in the recovery rate. We can do much better than go on storing people who won't respond because we didn't get to them fast enough."

Mr. FOGARTY. Is there anything else you would like to say, Doctor?

Dr. FELIX. I do not believe so, sir. I have tried to explain the budget as best I could. I would repeat what I said at the beginning—this is a sound budget which implements a broad program which we are now ready and capable of mounting. I sincerely hope that the committee will see fit to assist us by making funds available.

Mr. FOGARTY. I think you made a real good presentation—one of the best I ever heard you make.

EMPLOYEES IN STATE INSTITUTIONS AUTHORIZED TO ADMINISTER MEDICATION

There is one other thing I was going to ask. In State institutions, are there any standards or requirements concerning which employees may administer drugs?

In some State institutions, I have been told, orderlies who never went to medical school or a nursing school, but just got their knowledge by watching a doctor or a nurse, sometimes are the ones who give medication without any assistance from the professional person.

Dr. FELIX. I do not know of any State in which this is permitted. If it happens, it certainly is not permitted by regulation. I could do nothing else but most heartily condemn such a procedure. In every situation that I know of, including even the poorest State hospitals, drugs can only be administered on the order of a physician.

Now, in some case I know, nurses will administer certain kinds of drugs, particularly they will give those drugs that are given by mouth. They bring the pills to the patients and see that they are taken.

In some situations, they are not allowed to administer drugs that must be given by hypodermic needle. In others, they are allowed to administer some but not others. It depends on the kind of drug and the qualification of the nurse. A graduate nurse, who is experienced, and who is following very carefully written instructions with regard to medication, may in some cases, give medicine by hypodermic but certainly, under no condition that I can think of should an untrained person be permitted to give any medication at all to a patient.

Mr. FOGARTY. But I can see where it could happen in some of these State institutions, where it is almost impossible to get the necessary professional personnel, and maybe they just become lax over the years. I think that could develop in some institutions that I know about.

Dr. FELIX. I am sure this is true when you have a ward, let's say, of some old folks and you may have on the evening shift, I nurse for 200 or 250 patients and then there are some attendants. She could not get around with a bottle fast enough. Somebody else has to do it.

This is just absolutely reprehensible. I think a State which will permit this type of thing to happen, knowingly, is really derelict and I think the system, if permitted, should be roundly condemned.

Mr. FOGARTY. Thank you very much, Doctor.

Dr. FELIX. Thank you, sir.

INCIDENCE AND COST OF MENTAL ILLNESS

Statistics of the total current number of disabilities caused by each of the major diseases dealt with in the National Institute of Mental Health, and the estimated annual cost to the Nation.

I. DISABILITIES FROM MENTAL ILLNESS

Complete nationwide data are not available on the number of disabilities resulting from mental illness. The following is the number of patients receiving care for mental illness or mental deficiency in the various types of psychiatric facilities at some time during 1961. If it is assumed that each of these individuals

was disabled at some time during the year, this would then represent a minimum estimate of disability.

Type of facility:	Number of patients receiving care during 1961
State and county mental hospitals-----	783, 465
Veterans' Administration hospitals-----	124, 022
Private mental hospitals-----	80, 799
General hospitals with psychiatric facilities-----	209, 264
Public institutions for the mentally deficient-----	178, 460
Private institutions for the mentally deficient-----	8, 346
Outpatient psychiatric clinics-----	¹ 665, 000
Total-----	2, 049, 356

¹ Estimated, includes VA clinics.

NOTE.—These data are based on reports received by the National Institute of Mental Health from State agencies, hospitals, and clinics.

II. ESTIMATED ANNUAL COST TO THE NATION

A. Direct cost:

1. To Federal, State, and local governments for care of patients,
fiscal year 1962-----¹ \$1, 788, 003
2. To private agencies and individuals-----⁽²⁾

¹ Based on data received from Federal and State agencies.

² Not available.

HIGHLIGHTS OF PROGRESS IN MENTAL HEALTH RESEARCH 1962

ITEMS OF INTEREST ON RESEARCH STUDIES CONDUCTED AND SUPPORTED BY THE NATIONAL INSTITUTE OF MENTAL HEALTH

Problems of mental health and mental illness admit to no simple solution. The research attack on these problems cuts across a wide range of disciplines, drawing on the concepts and techniques of medical, biological, psychological, and social sciences.

It has become increasingly apparent that the etiology of mental disorders may be found in genetic factors or in metabolic errors, in psychological stresses and social experience, or in a combination of these factors. Consequently, clues to prevention, etiology, and treatment are being sought on all fronts—in the chemistry of the body as well as the nature of the mother-child relationship, in the dynamics of anxiety along with the mechanisms of the brain.

Eventual understanding of complex mental disorders depends upon an understanding of the normal as well as the abnormal. Knowledge of normal metabolism and of brain biochemistry, for example, is essential to an understanding of ways in which these processes may be defective in a disorder such as schizophrenia. Many basic studies are therefore devoted to the fundamental mechanisms involved in the brain and in human behavior. Other research focuses on the gathering of new knowledge about prevention, treatment, and rehabilitation.

Selected research findings of the past year are presented in this report. The research includes studies conducted in the Institute's own laboratories as well as in many nongovernmental research centers throughout the country that have received Institute support.

METABOLIC AND NEUROPHYSIOLOGICAL STUDIES

Thyroxine and protein synthesis

NIMH scientists determine point at which thyroxine effects protein synthesis.

Previous studies at the NIMH have shown that thyroxine stimulates protein synthesis. Recent findings have now established that the stimulation occurs in the transfer of soluble RNA-bound amino acid to microsomal protein. The investigators have further demonstrated that the thyroxine stimulation of the transfer step is not secondary to an effect on GTP, ATP, or GSR generation, the various cofactors for the transfer step.

The studies demonstrate that the thyroxine effect depends on the presence of both mitochondria and an oxidizable substrate and involves a lag of approxi-

mately 5 minutes preceding the period of stimulation. There is evidence that some intermediate substance derived from the interaction of mitochondria and thyroxine is formed during the lag period and is responsible for the stimulation of the protein synthesis. These requirements are the same as those for the effect of free amino acid incorporation into protein.

Previous research showed that thyroxine inhibits the rate of amino acid incorporation in adult rat brains but stimulates the rate in infant rat brains. Recent findings indicate that these differences are related to the mitochondrial fractions. Further, high amounts of amino acid incorporation into the protein of the mitochondrial fraction, particularly in preparations from infant rat brains, have been observed. Since this fraction as prepared in these studies also contained myelin, and myelin is known to be synthesized more rapidly in infant rat brains, studies have been initiated to determine if the amino acid incorporation reflects myelin synthesis *in vitro*. The effect of thyroxine in stimulating protein synthesis and its differential action on infant as opposed to adult brains could be related to the defective cerebral and intellectual development found in cretinism. (Drs. Louis Sokoloff, Seymour Kaufman, and associates. Reported in the *Journal of Biological Chemistry*.)

Isolation of particles containing transmitter agent

Successful isolation of tiny particles containing norepinephrine from sympathetic nerves in the rat heart and other tissue is reported by NIMH scientists.

Collaborative studies of this Institute and the National Institute of Neurological Diseases and Blindness had provided the basis for the present discoveries. Through these investigations, using electron-microscopic radioautography, norepinephrine was found to exist within sympathetic nerve vesicles. Furthermore, it was shown to act as a neurotransmitter in the sympathetic nervous system as does acetylcholine in the motor system.

This is the first time that any chemical mediator believed to transmit nerve impulses has been found in particles the size of synaptic vesicles in nerves. In the present studies, NIMH investigators using centrifuge techniques with homogenates of rat heart, glands, and other tissue, found isolated particles containing norepinephrine in the microsomal (lightest) layer of the tissue. These particles were much smaller than the heavy granules from adrenal medulla, known to store epinephrine.

These investigators and associates have further shown that norepinephrine is stored in at least two forms in the nerve and that these are affected differently by different drugs and are released separately. A small store of norepinephrine appears to be easily available whereas a larger store within the cell seems to be more tightly bound.

It thus appears that, once the readily available store is depleted, the drug (tyramine) that caused the release of norepinephrine no longer has an effect. The larger store seems to be released more slowly and by a different neurohormone.

These findings advance general knowledge of how the sympathetic nervous system functions and, in particular, help to explain the action of various drugs including many which act upon the heart and blood vessels. (Drs. Lincoln T. Potter and Julius Axelrod, NIMH. Reported in *Biochemical Pharmacology*, *Federation Proceedings*, and *Nature*.)

Ribonucleic acid new clue to protein synthesis

A new clue to the genetic factors controlling protein synthesis in the human body has been noted by NIMH researchers studying soluble ribonucleic acid (S-RNA).

Ribonucleic acid (RNA) is known to participate in the process by which the genetic information carried by deoxyribonucleic acid (DNA) determines the amino-acid sequence characteristic of each protein in the human body. Due to its relatively small molecular weight and short length, S-RNA, a special type of RNA, has proved particularly suitable for studies of protein synthesis.

Recent findings indicate that the average S-RNA molecule possesses a completely defined structure reproduced during synthesis in a highly specific manner.

Departing from the widely held concept that all the information necessary for protein biosynthesis is transmitted from parent to daughter cell only by DNA, investigators hypothesize that S-RNA is synthesized by pathways completely or partially independent of DNA. It also appears that at least part of the structure of the S-RNA is either identical or very similar for widely diverse classes of organisms.

The structure of S-RNA was studied through the use of T₁ ribonuclease which splits the S-RNA into small segments, at predetermined locations. Although the present data refer only to segments obtained by the action of T₁ ribonuclease, research conducted by the same investigators, using other ribonucleases, further supports the conclusion that a definite, nonrandom structure prevails throughout the S-RNA molecule.

A statistical analysis of the deviation of the structure of the S-RNA molecule from a completely random structure showed the average S-RNA molecule to be arranged in a nonrandom manner.

A completely defined structure for each S-RNA chain will aid in determining its amino acid specificity, its interaction with ribosomal RNA, and its function in recognizing the biological code which directs the formation of amino acid sequences in proteins. (Drs. Kilmer S. McCully and G. L. Cantoni, NIMH. Reported in the *Journal of Molecular Biology*.)

Mechanism for synthesis of methyl group donor in neurohormone production

New understanding of an important biochemical reaction is revealed through discovery by NIMH scientist of the mechanism for the synthesis of the methyl group donor important in this reaction.

The mechanism of the synthesis of the methyl group donor, (-)-S-adenosyl-L-methionine (AMe), important in a majority of the naturally occurring methyl transfer reactions in all forms of life and including the production of such neurohormones as epinephrine and choline, has been discovered by an NIMH scientist.

Although the important of AMe has been known for years, the mechanism of its synthesis has remained unexplained. Using a newly developed method of separation, the investigator discovered the intermediate steps in the enzymatic synthesis from ATP and methionine and presented a three-step pathway for the synthesis, catalyzed by the methionine-activating enzyme. The only intermediates involved in this pathway are bound to the enzyme with great specificity.

This reaction is one of the few proven cases where an enzyme, in this case the methionine activating enzyme, preferentially speeds up one direction of a reversible reaction, the synthesis of AMe, causing an experimental irreversibility of the synthesis. The tight binding of the products by the enzyme, found by the investigator to be one of the causes of the experimental irreversibility of the synthesis, may be applicable to other enzymatic reactions. (Dr. S. Harvey Mudd, NIMH. Reported in the *Journal of Biological Chemistry*.)

Serum protein factor in schizophrenia

Grantees have devised a new test for determination of serum protein factor.

NIMH grantees seeking to isolate unidentified protein factor in schizophrenics have developed a new biochemical test which has proved valuable as an indicator of the serum factor, as well as an indicator of metabolic disturbances.

The test is based on the ratio of lactic acid to pyruvic acid (the "L/P" ratio) in cells. Investigators found that chicken red cell metabolism in serum from schizophrenic patients showed an L/P ratio twice as great as that of cell metabolism in serum from normal subjects, thus suggesting the possibility of a biochemical "diagnostic" test for schizophrenia.

Preliminary findings in studies utilizing this indicator suggest that the serum protein factor may act as a regulator for complex biochemical mechanisms that control the release of energy in response of stress.

In tests with a patient population of 30 male chronic schizophrenics and 20 normal males as a control group, researchers found considerable day-to-day variations in the L/P ratios of the patients, while the normal group showed consistent ratios. This finding led to tests of serum extracted from both groups under conditions of minimum stress, when the subjects were asleep, for example, and under stressful conditions, when the subjects were required to exercise or take reaction time tests.

Under nonstressful conditions, serum taken from both groups was found to exhibit L/P ratios close to the normal range. However, under conditions of stress, the L/P ratios of schizophrenics showed substantial increases over those of control subjects. These findings suggest that the L/P ratio in schizophrenics is important in adaptation and maladaptation and may be produced by the patient's attempt to cope with stressful situations. Further research is underway regarding the effect of the serum factor on various enzyme systems.

Investigators, while unable to isolate the factor in its pure form, have determined that it is contained in the eugobulin fraction of serum proteins, that it

is extremely labile, yet can be stabilized by ascorbic acid or by an atmosphere of hydrogen. Significantly, three other groups of researchers using varied scientific techniques have arrived at similar findings.

The NIMH-supported study team has pioneered the development of a new technique of serum extraction from plasma making possible a tenfold increase in the amount of serum obtained. The new technique should greatly facilitate research in this area. (NIMH Grantees Dr. Gottlieb, Frohman & Associates, Lafayette Clinic, Detroit. Reported at the Second International Conference on the Biological Treatment of Mental Illness.)

New insights on auditory mechanisms

Recent studies by NIMH scientists have thrown new light on the mechanisms involved in the process of hearing.

Although the nervous system is the principal organ of adaptation, little is known about the internal mechanisms on which this accommodation depends. In a series of current studies on central nervous system mechanisms involved in audition, investigators have pursued a new approach in which animals are introduced to loud sounds to a period of hours to observe accommodative changes occurring in the known auditory pathways throughout the central nervous system. The experimental analysis extends into the period of recovery following discontinuation of the loud sounds. The sound level of exposure is roughly equivalent to that at a noisy street corner and does not produce any tissue damage in the ear or nervous structures. Central nervous activity is recorded continuously.

Dynamic adjustments have been observed to take place both during and following the loud sound exposure, and involve changes lasting up to a few hours. The introduction of anesthetic or neurosurgical interventions reveal that the adjustments are controlled by nervous system mechanisms. Some of the changes imply a protection of higher centers from overoccupation with environmental stresses. Others seem to reflect a "learning" process of adjustment to environmental changes that requires time to be established, and then has a "momentum" that persists even after the environment has returned to normal. (Drs. Arnold Starr and Robert B. Livingston, NIMH. Reported to the American Physiological Society.)

New technique for study of chemical susceptibility of cells

An NIMH scientist has developed a technique for electrophoretic application of minute amounts of chemical substances to brain cells.

There has long been suggestive evidence for the chemical inhomogeneity of cell populations within even quite small areas of the brain. A new micropipette technique developed by an NIMH scientist opens the way for systematic analysis of the chemical susceptibilities of individual cells in various regions of the central nervous system.

Thus it is now possible to map the characteristics of cell populations in areas of the brain which may be directly concerned with the steering mechanisms of autonomic functions, such as respiration and maintenance of blood pressure, as well as the storage, and release of genetically coded and emotionally charged forms of behavior, including hunger, thirst, aggression, and sex.

An analysis of the chemical susceptibilities of cells in the brain stem of the cat, using a 5-barrel micropipette and involving some 800 cells, has already shown that not all cells are uniformly responsive to acetylcholine, a substance which has long been regarded as a chemical mediator in peripheral autonomic nets. Of all cells studied, about 75 percent failed to change their rate of discharge in response to the substance. Approximately 25 percent consistently increased and five percent consistently decreased their activity during or just after administration of acetylcholine. Differential response patterns are also being observed with such other substances as epinephrine, norepinephrine and serotonin. Studies now underway as part of a long-term program are exploring the chemical susceptibility of other areas of the brain such as the olfactory bulb and the hypothalamus. (Dr. Gian Salmoiraghi, NIMH Neuropharmacology Research Center. Reported to Collegium Internationale Neuro-Psychopharmacologicum.)

Central neural circuit in thirst drive

NIMH grantees have found that primary drives, such as drinking or eating, are mediated by circuits in the brain rather than by the response of single or isolated loci as heretofore believed and that a circuit is both structurally and biochemically distinct for a particular drive.

Continuing from previous findings establishing the correlation of drinking behavior with the application of cholinergic drugs to a specific locus in the brain, NIMH grantees investigators sampled other brain areas in rats for this response. Although the correlation between drinking and cholinergic stimulation of the brain is recognized to be remarkably specific, they found a number of positive areas for drinking, identified by them from brain sections of their animal subjects. These areas were found to lie within the positive reinforcement system traced by Olds and others in rats in self-stimulation experiments and appeared to be included within the proposal outlined by Papez in 1937 which states that a series of structures of the brain composed an interconnected, functional circuit related to the expression of emotion in man and animals. The brain areas found by these investigators to be positive for the drinking response are either part of the original Papez circuit or closely integrated with it.

These investigators suggest from their findings that a functional neural circuit can be traced through a selective sensitivity to a chemical agent or to a particular range of concentration of that agent. Their previous research showed little indication that entire circuits or their synaptic interconnections might be biochemically distinct. They feel their data suggest that circuits mediating each of the primary drives may be found to follow generally parallel courses through the limbic system and diencephalon and that separate functional circuits will be able to be traced through specific chemical keys or stimulation techniques. (NIMH grantees, Dr. Alan E. Fisher and John N. Coury, University of Pittsburgh. Reported in Science.)

PSYCHOPHARMACOLOGY

Effectiveness of drugs on schizophrenia

Three active phenothiazine drugs proved substantially more effective than placebos in treating acute schizophrenia, according to comparative studies supported by the NIMH Psychopharmacology Service Center.

Chlorpromazine, thioridazine, fluphenazine, and placebos have been tested for effectiveness in the study which so far has involved tests with 350 patients in 9 hospitals. All three drugs appear to be nearly identical in therapeutic effects. Each seems to affect all aspects of schizophrenic pathology rather than being particularly effective on one or two target symptoms.

Generally, although fluphenazine appears to cause the highest incidence of neurological side effects and thioridazine the lowest, these differences are not as striking as had been supposed previously. Nonneurological side effects appear to be more frequent with thioridazine than with fluphenazine.

Preliminary analyses have failed to establish that the type of hospital has any clear effect on patient response to either drugs or placebo.

In another study supported by the psychopharmacology service center, new drugs are being clinically evaluated to determine their potential value in the treatment of psychiatric disorders. Approximately 115 different drugs have been studied thus far in 15 hospitals.

Among new classes of compounds under investigation are the benzoquinolizines and phenylpiperazines. These are being evaluated for their tranquilizing activity as a demethylated form of certain antidepressants, amitriptyline and imipramine, to determine whether the new compounds have advantages over the parent compounds.

Investigators have found that a derivative of phenothiazine, eninthatate, appears to be an injectable form of this compound with pharmacological effects that persist for about 2 weeks when the drug is injected in fatty deposit areas of the body. The fact that effects remain for this period of time suggests that the drug might be valuable in treating patients who fail to take their medication regularly. It also has potential usefulness in aftercare drug therapy; discharged schizophrenics, for example, could receive the drug as outpatients at regular intervals. (Drs. Jonathan Cole, Solomon Goldberg, and Dean Clyde, NIMH. Presented to American Psychiatric Association.)

Effect of psychotropic drugs on urinary catecholamines in man

Reserpine and chlorpromazine have been found to cause changes in VMA excretion.

NIMH scientists studying effects of six psychotropic drugs on urinary excretion of vanillylmandelic acid (VMA) in normal volunteers at NIH found that only reserpine and chlorpromazine caused changes in VMA excretion, indicating altered catecholamine metabolism.

The effects of the psychotropic drugs on the urinary excretion of VMA, the major product of catecholamine metabolism, were studied through a highly specific method developed by the investigators. The six drugs consisted of three tranquilizers, reserpine, chlorpromazine, and meprobamate; a narcotic, morphine sulfate; a hypnotic, pentobarbital sodium; and a cerebral stimulant, d-amphetamine sulfate.

The study revealed that of these drugs administered to 16 normal volunteers in single, clinical doses, only two, reserpine and chlorpromazine, were associated with a consistent and unequivocal effect on VMA excretion. Reserpine caused an increase and chlorpromazine a decrease in VMA excretion independent of any related change in kidney function as determined by endogenous creatinine excretion. Morphine sulfate caused a decrease in VMA excretion followed by an increase. These changes, however, were paralleled by changes in endogenous creatinine excretion, indicating the effect of morphine on VMA excretion was not a manifestation of altered catecholamine metabolism.

Through measurement of urinary tryptamine excretion, the investigators have shown for the first time in man that d-amphetamine causes no monamine oxidase inhibition, thus disproving a widely held theory that this is the mechanism by which amphetamine causes cerebral stimulation. It is evident that there is no consistent relationship between the rate of catecholamine metabolism and the observed clinical effects of the psychotropic drugs tested. Dr. Roger K. McDonald and Mrs. Virginia Weise, NIMH. Reported in the *Journal of Pharmacology and Experimental Therapeutics*.)

Metabolites of tranquilizers

New evidence indicates that metabolites of tranquilizers may contribute to the drugs' overall effects.

NIMH studies on the metabolism of the phenothiazine tranquilizers, especially chlorpromazine and promazine, suggest that, at least in animals, their overall effects may be due in part to some of the metabolites of the parent drugs—demethylated, hydroxylated, and demethylated hydroxylated metabolites in particular.

Previous evidence indicates that not all drugs are detoxified or inactivated by metabolism. Some drugs, in fact, may be converted to metabolites which are more toxic or more active than their parent drugs. The present study was conducted to determine whether or not any of the many potential metabolites of chlorpromazine and promazine might contribute to the activity of the parent drug.

The effects of seven compounds were compared in four pharmacological and behavioral tests on rats and mice. The compounds included: chlorpromazine monomethylchlorpromazine, chlorpromazine sulfoxide, chlorpromazine-N-oxide, promazine, 2-hydroxypromazine, and 4-hydroxypromazine. The tests involved the effects of these compounds on potentiation of hexobarbital sleeping time, on stimulated activity (rotating rod), and on conditioned response situations controlled by either reward or punishment.

In all tests, chlorpromazine sulfoxide was the least active of the compounds. Chlorpromazine-N-oxide, although active, was less active than chlorpromazine or monomethylchlorpromazine. A lag in onset of activity, which was not seen for any of the other drugs, was noted with chlorpromazine-N-oxide in both conditioned response tests. Monomethylchlorpromazine was generally only slightly less active than chlorpromazine.

In the promazine series, 4-hydroxypromazine was about equally as active or somewhat less active than promazine. 2-hydroxypromazine was markedly less active than promazine except in the sleeping time test when administered intravenously. In this case, it was about as active as promazine. Promazine was less active than chlorpromazine in all tests.

Although not all of the compounds tested represent actual metabolites, they serve primarily as models and provide important preliminary information on this type of derivative. Synthesis of phenolic derivatives related to chlorpromazine and promazine, presently not available, is being attempted. (Drs. Herbert S. Posner, Eliot Hearst, and George J. Cosmides, NIMH, and Wilson L. Taylor, St. Elizabeths Hospital. Reported in the *Journal of Pharmacology and Experimental Therapeutics*.)

Effect of antidepressants on frog pigmentation

An NIMH grantee has found that certain nervous system stimulants suppress pigmentation in the frog under conditions when pigmentation would normally occur.

Findings suggest that alteration in frog pigmentation may serve as a biological indicator of the activity of various psychoactive drugs used in the treatment of depression.

In the frog and other animals the stimulus for pigmentation is the melanocyte-stimulating (darkening) hormone of the pituitary gland. This hormone has been shown to be present in a wide group of vertebrates, and recently its influence on human pigmentation has been demonstrated.

The present study describes the reactions of five antidepressants—two psychamine drugs, amphetamine and methylphenidate, and three drugs possessing monamine oxidase (MAO) inhibitor properties, pheniprazine, phenelzine, and iproniazid. All five are used clinically in the treatment of the mentally depressed state and, in the case of the MAO inhibitors, cardiovascular disease as well. Each of these drugs, injected in light-adapted frogs, suppressed pigmentation which normally occurs when the frog is transferred to a dark background. Of the psychamine drugs used, amphetamine proved to be the more potent suppressor. Of the MAO inhibitors tested, pheniprazine was the most active.

The action of the psychamine drugs in preventing pigmentation may be related to their structural similarity to norepinephrine, a potent suppressor. It is postulated that the effectiveness of the MAO inhibitors is due to their enzyme-inhibiting properties which result in an increase in the levels of physiologically active amines such as norepinephrine and serotonin. It was also noted that another central nervous system antidepressant, imipramine, which possesses neither sympathomimetic nor MAO inhibitor properties, caused a darkening of the frog rather than suppression of pigmentation found with the other antidepressants. Previous findings indicate that pigment change such as that observed with imipramine is characteristic of several tranquilizers including meprobamate, reserpine, and the phenothiazines. (NIMH grantee, Dr. George R. Scott, Oberlin College and Woods Hole Marine Biological Laboratory. Reported in *Nature*.)

Action of hypotensive drugs

A study of the effects of two drugs, bretylium and guanethidine, known to produce hypotension in animals and in man, indicates that hypotensive drugs exert their action by affecting the uptake and release of the hormone noradrenaline.

NIMH scientists have found that the drugs block both the release of noradrenaline after stimulation of sympathetic nerves and the release of noradrenaline by reserpine. Rats and cats were injected to determine the effects of bretylium and guanethidine on the uptake and the spontaneous and reserpine-induced release of noradrenaline in the rat heart and in the stimulated and unstimulated splenic nerve endings of the cat.

These investigators showed that these two drugs reduce the reserpine-induced release of noradrenaline in the rat heart and that guanethidine blocks the release of noradrenaline following stimulation of the splenic nerve of the cat. Other investigators have previously shown that bretylium produces the same effect on the splenic nerve. These observations indicate that the release of noradrenaline by reserpine is dependent on sympathetic nerve impulses.

Bretylium inhibition of noradrenaline release by reserpine was similar to that produced by monamine oxidase inhibitors, yet bretylium did not inhibit monamine oxidase. Bretylium blocked both the release and the uptake of noradrenaline, causing no change in the endogenous noradrenaline concentration in the rat heart while the monamine oxidase inhibitors prevented the release of noradrenaline and increased the endogenous noradrenaline concentration. (Drs. G. Hertting, J. Axelrod, and R. W. Patrick, NIMH. Reported in *British Journal of Pharmacology and Chemotherapy*.)

Twofold effect of new compound

NIMH grantees have found a substituted pyridindole capable of enhancing the stimulating action of amphetamine and of prolonging the central depression induced by certain barbiturates and ethanol.

These twofold effects are from a new pharmacological substance related to the naturally occurring Harmala alkaloids. Injection of the new compound—3,5-dicarbomethoxy-1,2,3,4-tetrahydro-2-methyl-9H-pyrid[3,4-b] indole (II)—even in minute amounts, was found both to double the sleeping time of animals under the influence of barbiturates (pentobarbital and hexobarbital) or ethanol, and to intensify greatly the stimulatory effects of amphetamine on "spontaneous" activity in mice. Of particular note was the finding that when this substituted

pyridindole was administered alone, even in large doses, it exhibited no stimulatory effect.

The nature of the animals' recovery from the barbiturates in the presence of the substituted pyridindole was not significantly different from that induced by the barbiturates alone. Thus, the compound, the investigators state, does not appear to affect sleeping time in the manner of monamine oxidase inhibitors. Furthermore, the compound does not exert its influence in the same way as do certain tranquilizing agents. As opposed to the behavior of chlorpromazine and reserpine, for example, it does not reinduce sleep in animals just recovered from hexobarbital. For the present, the investigators have classified the substituted pyridindole with a number of other substances reported to prolong barbiturate depression by undetermined mechanism. (NIMH Grantees Drs. Louis S. Harris and Frederick Uhle, Harvard Medical School. Reported in the *Journal of Pharmacology and Experimental Therapeutics*.)

Response of schizophrenics to phenothiazine derivatives

Acetophenazine was found to be the drug of choice for paranoid type schizophrenics and perphenazine for nonparanoid schizophrenics in recent grantee studies.

The findings in comparative studies of these two phenothiazine derivatives add to knowledge about the effectiveness of drugs on specific types of symptoms. Both drugs were administered over a 6-week period to 110 newly admitted schizophrenic patients in 5 Veterans' Administration hospitals. Both produced general improvement in the patients as a whole. However, investigators noted that response to perphenazine tended to be uniform and predictable while response to acetophenazine varied considerably. The greatest extremes in response, from patients who improved most to patients who improved least, occurred in the group treated with acetophenazine.

The widely varied response led to further study, focusing on the drugs' effectiveness on specific psychiatric symptoms. Using rating scales, researchers divided all patients into two groups: the paranoid type, exhibiting anxiety, tension, suspiciousness, and unusual thought content, and the nonparanoid type, characterized by conceptual disorganization, withdrawal, and blunted effect.

When the drugs were evaluated for effectiveness on these types of symptoms, clear differences emerged. Paranoid-type patients showed definite improvement under treatment with acetophenazine, while nonparanoid types did not, indicating the former as the drug of choice for paranoid-type patients.

Researchers point out that the classification of patients by rating scales, as in this study, does not necessarily correspond to their clinical diagnosis; in fact, when clinical diagnosis was used as a basis for grouping the patients, no significant differences in response to either drug were noted. This suggests that at least a part of past difficulty encountered in the search for drug-diagnosis interactions has stemmed from confusion in defining diagnostic types. (NIMH Grantee J. E. Overall, Kansas State University, and associates. *Clinical Pharmacology and Therapeutics*.)

Psychotropic drug use by physicians in prepaid medical plan

An NIMH team found that psychotropic drugs were prescribed in 5.1 percent of patient-physician visits, and that only 27 percent of these drugs were for psychological symptoms.

Using the facilities of Group Health Association of Washington, D.C., a prepaid medical plan, investigators studied factors associated with prescriptions of psychotropic agents by nonpsychiatric physicians.

A retrospective examination was made of the medical records of GHA patients for whom a psychotropic agent had been prescribed during July and October of 1958 and January and April of 1959. About 75 percent of the psychotropic prescriptions written were for tranquilizers, and about one-fourth were for anti-depressants. Only 27 percent of the psychotropic prescriptions were used to treat psychological or psychophysiological symptoms. The remainder of the prescriptions were used for organic indications: for example, promethazine for respiratory infections, and reserpine for hypertension.

Psychotropic drugs were prescribed at a higher rate for females than for males. This was particularly true for the amphetamines and the amphetaminelike substances, which were used by the obstetrician-gynecologists to control weight gain in their pregnant patients. Age differences included: low frequency of psychotropic prescriptions to patients under 19 and over 70; more frequent use of antihypertensive agents for those in the 40-69 age group. Physician specialty

groups were found to vary in their use of types of psychotropic agents. This variation may be accounted for by the different organic symptoms treated by the specialty groups.

Because of the specialized nature of the study setting, the relationships discovered can be generalized only in a limited fashion. The surprisingly low use of psychoactive agents to treat psychological symptoms may reflect a tendency of nonpsychiatric physicians to record only the organic symptoms presented by the patient, despite the physician's awareness of coexisting psychological difficulties. (Drs. Seymour H. Baron and Seymour Fisher, NIMH Psychopharmacology Service Center. Reported in Public Health Reports.)

PSYCHOBIOLOGICAL STUDIES

Adaptation to stress in Project Mercury astronauts

NIMH studies of the U.S. astronaut team indicate that the pilots reacted to the psychological stresses of space flight by mobilizing their already well-developed defenses, and that physical stresses were less than anticipated.

Research into the degree of stress in space flights and the mechanisms for maintenance of adaptive behavior under stress was undertaken at the request of the National Aeronautics and Space Administration. Data are still being analyzed but preliminary findings show that postflight psychometric test performance did not differ importantly from control levels.

The study covered three phases: personal interviews early in Project Mercury training; a battery of tests measuring emotional state, intellectual functioning, and endocrine functioning, administered during the training period; and a repetition of the same test battery immediately before and after flight, as part of more detailed studies of flight effects.

General findings to date indicate that the astronauts met psychological stress situations, such as a flight being "scrubbed," by intensifying their usual defenses. For example, investigators concluded that scrubbed flights or long delays in countdowns had no adverse psychological effects because the pilots were ambitious, strongly motivated men who had attained their major goal in being chosen for the flight and hence when it occurred was much less important to them.

Researchers noted a lack of acute anxiety prior to flight. Concern with physical harm or death was present but these feelings were effectively isolated and secondary to the focal threat felt by the men, the possibility of failure. Data indicate that the pilots reacted to this threat by heightened activity. They focused on the task at hand, tried harder to perfect their skills and learn more about the project, and in general concentrated upon buttressing their already high competence by further achievement.

The physiological stresses of flight, including reaction to heat, acceleration, and weightlessness, proved to be less important than had been anticipated. Researchers suggest that questions of physiological stress tolerance should be less emphasized in the future selection of astronauts.

On the other hand, reviewing the initial selection procedure in the light of knowledge gained through the flights, they feel that future selection procedures should emphasize a broad knowledge of space sciences and a high level of technical ability, since the pilots must contribute to the development of their space vehicle, its components, and supporting systems.

Investigators point out that the Mercury team was so homogeneous and uniformly well qualified that it is difficult to pinpoint relationships of aptitude or intelligence to successful performance in the flights. The major factor in predicting success seems to be the individual's successful past performance in analogous jobs, as test pilots, etc. (Dr. Sheldon J. Korchin, NIMH, and Dr. George E. Ruff, University of Pennsylvania. Reported to the American Psychological Association.)

Hypnosis in study of FFA response to emotional stress

The use of hypnosis has made possible NIMH studies which indicate that depression, fear, and anger increase the level of free fatty acids in the bloodstream.

Although previous research had shown that anxiety stimulates an increase in the free fatty acids (FFA), the NIMH study marks the first time that an FFA response has been observed in connection with depression and anger. Investigators used hypnosis to overcome distractions and situational complications which ordinarily interfere with attempts to study human emotions in a

laboratory setting. Through hypnotic suggestion, they were able to arouse emotions almost instantly in volunteer subjects and to correlate the FFA changes which occurred.

FFA is the form in which fat goes from fat depots in the body, via the bloodstream, to organs which burn it. Levels of FFA change rapidly, affording sufficient magnitude of response for study, and only a small blood sample is required.

Of the 16 pretrained volunteers used in the study, 10 were able to distinguish varying degrees of sensory distortion under hypnosis. For all 10, significant FFA increases were observed in 1 or more emotional categories after hypnotic suggestion. Three of these subjects showed significant FFA responses to two of the three emotional states induced. All 10 subjects reported undergoing intense emotions accompanied by associated fantasies or memories; the most susceptible frequently reported that the emotions aroused equaled anything they had experienced in the past.

Those subjects unable to experience sensory distortions under hypnosis showed no FFA response to the induced emotions, demonstrating that the ability to experience such distortions under hypnosis is correlated with the ability to respond physiologically to hypnotic suggestions of emotions. Investigators point out that previous psychosomatic studies often failed to take into account either this crucial difference in selection of subjects or the ability of subjects to respond to one emotion but not to others.

In only one emotional state, anger, was there a close correlation between FFA rise and the intensity of the emotion. A rise in FFA was induced in connection with fear and depression but the increase was not in direct ratio to the intensity of the emotions. Investigators suggest that the component of anger in depression may contribute to the FFA rise noted in this emotional state. (Drs. Peter Mueller and Jacob Fishman, and Victor Stoeffler, NIMH. Reported to American Psychosomatic Society.)

Stress response of rats handled during infancy

An NIMH grantee reports that rats handled in infancy respond to acute stress with a significant elevation of circulating corticosteroids in the blood as compared to their nonhandled counterparts.

The investigator studied the response of manipulated and nonmanipulated infant rats to an acute noxious stimulus in adulthood, the response being the amount of corticosterone present in the blood. It was found that within the time limits investigated after the challenging stimulus (electric shock), the level of circulating steroids remained significantly higher in manipulated rats than in those not manipulated.

Heretofore, various investigators proposed that infantile handling of an animal produces resistance to stress because the observed physiological response to a challenging stress stimulus appeared to be less vigorous. It was observed, for example, that significantly less hypertrophy of the adrenals of animals handled in infancy compared with nonhandled animals followed such stress as daily exposure to fear-producing stimuli. Further, handled animals were found to survive for longer periods of time under conditions of prolonged food and water deprivation than nonhandled animals.

The investigator points out that the nature of the response appears to vary not only with infantile handling or the lack of such handling but also with the nature of the stress conditions—that rats manipulated in infancy appear to make a more rapid and greater response to acute stressful conditions such as observed in this study, whereas nonmanipulated animals appear to make a greater response if the stress conditions are chronic such as daily fear stimuli or prolonged food and water deprivation. He therefore proposes that his findings do not support the general thesis that infantile manipulation makes an animal less responsive to stress but that it appears to impart to the animal a capacity to respond “more appropriately” to the demands of the environment which include stress. (NIMH grantee, Dr. Seymour Levine, Stanford University. Reported in “Science.”)

Differential diagnosis of depressive disorders

NIMH grantees have developed a simple, reliable method to differentiate psychotic from psychoneurotic depressed subjects while under sedation.

Previous research has indicated that identification of the point at which an individual becomes sedated when receiving intravenous sedative is a reliable measure of manifest anxiety and an objective method for the differential diag-

nosis of depressive states. Difficulty has been encountered, however, in identifying the point of sedation for some patients and in duplicating the results in general.

Under study was the possibility of using the galvanic skin reflex (GSR) as an index of sedation. GSR is the measurement of the electrical reactions on the skin as detected by a sensitive galvanometer. It is believed to be correlated with emotion, effort or strain. Recordings were made on each of 38 subjects for the strength of electrical discharge present on the surface of the skin throughout the course of administration of sodium thiopental. The group tested consisted of 20 young normal subjects, 10 subjects previously diagnosed as psychoneurotic, and 8 as psychotic.

During the sedation process, it was observed that the skin conductivity decreased steadily and that GSR amplitude underwent an initial decrease followed by a brief, paradoxical rise and then fell to approximately zero (the inhibition threshold) after which the GSR curve remained flat. For the series of subjects tested, it was found, the GSR inhibition threshold for the psychotic individual was reached with significantly less dosage of sedative than was needed for the psychoneurotic group. No significant difference in the dosage needed was observed between the psychoneurotic and normal subjects to reach this point in the GSR curve.

The investigators conclude that this preliminary study indicates that the measurement of the GSR inhibition threshold is a simple and objective method that appears to differentiate psychotic from psychoneurotic depressed subjects with a high level of reliability. (NIMH grantees, Dr. Mario Perez-Reyes and associates, Department of Psychiatry, University of North Carolina School of Medicine. Reported in "Psychosomatic Medicine.")

Role of peer affection in social adjustment

The effect of total social isolation in infancy on the personal-social behavior of adolescent and adult rhesus monkeys is a function of the duration of social deprivation, NIMH grantees have found.

Monkeys subjected to total social isolation in which they saw no other monkeys, adults or infants, and no people for 2.5 months showed temporary social difficulties but subsequently fully recovered as reflected in social, sexual, and intellectual performances when the animals were allowed social contacts. However, total social isolation for 6 months, 1 year, and 2 years destroyed potentiality for social adjustment, there being little or no recovery or development of normal social functioning. No permanent intellectual loss was demonstrated, and it is apparent that learning capability may be left intact after all social potentialities are obliterated.

Investigators compared the behavior of groups of monkey infants raised by real monkey mothers and raised on cloth surrogate "mothers." All infants were allowed to play with each other 2 hours a day. The babies raised by real monkey mothers began playing together at an earlier age and more effectively than those raised by surrogates, but differences between the two groups lessened and gradually were obliterated in the second year of life. Similarly, normal heterosexual behavior appeared earlier in the babies raised by monkey mothers than in those raised by surrogates. However, these differences disappeared early in the third year of life.

These data, taken in conjunction with the results from additional groups of monkeys raised with access to each other but without mothers or with only surrogate mothers, lead to the conclusion that real mothering can facilitate early social development but is not essential to attainment of normal personal-social adjustment. On the other hand, infant-infant experiences in the first half year of life appear to be *sine qua non* for later adjustment. (NIMH grantee, Dr. Harry Harlow and associates. Reported at American Academy of Psychotherapists.)

PROGRESS IN TREATMENT

Largest decrease in patient population

Fiscal year 1962 marked the largest single-year decrease in number of patients resident in public mental hospitals, data from NIMH Biometrics Branch reveal.

Changes in resident population of public mental hospitals result from the combined effect of admissions, net releases, and deaths during the year. Despite a marked increasing trend in total admissions and net releases, the number of persons resident in these hospitals on any one day has steadily declined. Fiscal

year 1962 marked the largest single year decrease since the downward trend began in 1956, according to data collected by the NIMH Biometrics Branch.

A total of 515,948 patients were resident in 286 public mental hospitals at the end of fiscal 1962, a decrease of 11,587, or 2.2 percent, from the comparable figures for fiscal 1961.

Total admissions to these hospitals for 1962 were 270,767, an increase of 17,762, or 7 percent, over 1961. Net releases for 1962 totaled 230,899, up 7.1 percent over the 1961 net release figures.

This continuing decline in the number of patients maintained for long periods in public mental hospitals is attributable to such factors as more intensive treatment services available in these hospitals and more effective use of drug and other therapies, as well as the increased availability of community resources for treatment and aftercare of these patients.

Increase in outpatient psychiatric clinics

The number of patients treated in outpatient psychiatric clinics in the United States rose to 665,000 in 1961, as compared to 502,000 in 1959, according to data collected by the Biometrics Branch of the NIMH.

The number of clinics increased from 1,429 in 1959 to 1,568, and the ratio of clinical man-hours of service per 100,000 population rose to 166, up from 149 2 years ago, the study revealed.

The report shows that the ratio of man-hours of professional service has steadily increased, with an average gain of about 6 percent a year since nationwide reporting began in 1954. The number of patients seen increased at a faster rate than hours of service, indicating an average gain of 14 percent. The number of patients treated in outpatient clinics reached 366 per 100,000 population in 1961. As measured against the goal of 1 fulltime clinic per each 50,000 population, suggested by the report of the Joint Commission on Mental Illness and Health, the goal, nationwide, is only 60 percent achieved.

In a detailed study of patients seen at these clinics between 1955 and 1959, investigators found that children between the ages of 14 and 17 made up the largest group per 100,000 population. Among adults, those between 30 and 44 comprised the largest group of patients. Smallest categories were those for preschool-age children and the aged. Psychoneurotic disorders, psychotic disorders, and personality disorders predominated among adults, while the largest diagnostic category among children was transient situational personality disorders (adjustment reactions).

Other findings were that clinic services tend to be brief, with four being the median number of interviews for both children and adults. One-fourth of the children were withdrawn from clinic services, one-half referred to other agencies, and one-third terminated without referral. Among adults, about two-fifths withdrew, one-third were referred elsewhere and one-fourth terminated without referral.

The large proportion of patients who withdraw from clinic services reveals a need for followup studies of these persons to determine whether their withdrawal represents a missed opportunity on the part of the clinic or an indication that the patient considered his problem alleviated. (Vivian B. Norman, Beatrice M. Rosen, and Dr. Anita K. Bahn, NIMH. Reported in "Mental Hygiene.")

Insurance for short-term outpatient psychiatric care

Results of NIMH-supported research indicate that extending health insurance benefits to include short-term ambulatory psychiatric care is economically and medically sound.

Group Health Insurance, Inc., of New York City, in a project also sponsored by the American Psychiatric Association and the National Association for Mental Health, extended the insurance of a sample of 30,000 subscribers and their 46,000 medically insured dependents to include a large part of the costs of obtaining short-term psychiatric care. Costs of providing this extended coverage without an increase in premiums was underwritten by NIMH grant funds for a 30-month period from June 1959, to December 1961. Benefits offered for any condition treated by a psychiatrist included up to 30 days hospitalization, psychological testing, and up to 15 office visits to participating psychiatrists.

Psychiatric claims were filed for 1,077 of the 76,000 persons covered during the 30 months of the project. The overall rate of use was 12.2 cases per 1,000 during 2 years of operation. The rate of new cases per 1,000 covered persons was highest during the first 6-month period. The cost per terminated case averaged \$186.

Demographic subgroups of the eligible population varied widely in their use of psychiatric benefits. Utilization rates of college graduates were three times that of high school graduates. Other groups with a high utilization rate were: the divorced, clerical and professional workers, adults with family incomes below \$2,000 and over \$10,000, and adults between 20 and 39 years.

Psychiatrists were available, interested, and cooperative. Many of the participating psychiatrists never saw a project patient because there were not enough patients to go around. Those who became involved cooperated well in helping to fulfill the research objectives of the project. Project patients were comparatively high users of medical-surgical services. Over a 3-year period, their GHI claims per person averaged 176 percent of the nonpsychiatric patients' claims for medical-surgical services.

Half the office patients used the maximum benefits. Of those who used maximum office benefits, more than half continued treatment privately. Though psychiatrists usually thought further treatment would help their patients, they regarded 3 out of 4 patients as recovered or improved at the termination of project benefits. (Helen Hershfield Avnet, Group Health Insurance, Inc., in "Psychiatric Insurance," GHI, 1962.)

Aftercare program in a community clinic

Maintenance drug therapy has been found effective in patients' readjustment to the community.

In a followup study of discharged schizophrenics participating in an aftercare clinic program, NIMH grantees found that maintenance drug therapy was safe and effective in easing readjustment to the community and did not interfere with job performance or learning ability. When relapse occurred, treatment in a day hospital proved more effective than rehospitalization in controlling symptoms quickly and expediting discharge.

The 5-year study, partially supported by an NIMH grant, focused on several unselected groups of 100 patients each seen by the research unit of the Manhattan Aftercare Clinic. Virtually all chronic patients—those whose hospitalization had been prolonged or who had several admissions—required drug therapy over considerable periods of time. In a number of cases, patients who had adjusted well under maintenance therapy for 4 years or more quickly relapsed when drugs were discontinued; when drugs were reinstituted, overt symptoms were again brought under control.

Maintenance therapy was found to be particularly necessary when patients were facing stressful life situations, such as the excitement of returning home. Symptoms would reappear during those times unless therapy was instituted. Once the patient had become accustomed to a new routine, this emergency therapy could be reduced safely to minimum levels.

To test the efficacy of various treatment settings, patients showing severe psychotic relapse were divided into two groups, one of which was rehospitalized while the other was treated in a day hospital. In the vast majority of cases, control of symptoms and discharge from the facility was accomplished in 2 to 4 weeks for the day hospital patients, while rehospitalized patients required treatment for 3 to 12 months and occasionally for far longer periods.

About 35 percent of the patients proved able to find employment on their own initiative and only about 10 percent needed vocational rehabilitation either to acquire work tolerance, learn new skills, or brush up on old ones. The majority were able to return to occupations similar to those they had followed prior to hospitalization. Although 65 percent of the employed patients were on drug therapy, the medication did not interfere with their job performance or learning ability and did not make them accident prone.

During the study period, 17 of the women patients became pregnant and 3 gave birth twice. All the children born to mothers who were on drug therapy showed normal development; psychological tests revealed normal intelligence and showed no pathological findings.

The aftercare clinic staff maintained close personal contact with the patients and provided continuing assistance throughout the study period. Investigators believe that this continual help and reassurance figured importantly in the low return rate. On the basis of study findings, researchers conclude that adjustment of drug dosage and prolonged assistance to the patient are essential if an aftercare program is to provide the basis for a solid community adjustment (Dr. Else B. Kris, New York State Department of Mental Hygiene, reported in *American Journal of Public Health*).

New technique in studying marital conflicts

NIMH investigators have developed an experimental technique which uses color samples as a tool in assessing the way husbands and wives cope with marital conflicts.

Findings indicate that there are characteristic styles of coping with conflict which may be identified and used as a basis for future research into husband-wife and parent-infant behavior patterns.

The method, called the color-matching technique, was used in an experiment involving 50 couples. Each husband and wife separately compared a color card with a set of similar cards representing slight gradations in color and decided which was the closest match. Then the couple was asked to agree mutually on the best match in each case. Ten of the twenty samples presented to husband and wife, while apparently identical, actually differed in a manner not readily discernible.

As the couples attempted to resolve their disagreements over the samples which had built-in contradictions, meaningful differences were noted in their methods of coping with the conflict. Some could tolerate the situation only briefly while others tolerated uncertainty well and jointly explored a diversity of alternative solutions. Some were able to consider only those alternatives suggested by the instructor. Others showed an ability to "step back" from the situation and to consider alternative solutions of their own.

Two aspects of coping style were considered particularly important, in terms of solving the test conflict. The first was the ability to achieve perspective, shown in the color test as the capacity to consider hidden elements in the situation as an explanation of the disagreement.

The second factor was the maintenance of esteem for self and spouse throughout the conflict. Where such mutual trust and esteem was lacking, the result was discouragement and disparaging comments about self or spouse, which tended to widen the area of disagreement and turn the conflict into a power struggle between husband and wife.

Researchers believe that the color-matching technique, since it helps identify characteristic styles of coping with puzzling or ambiguous situations, may be useful in predicting how well couples will be able to adjust to new life situations, such as the first pregnancy, as they appear in a developing marital relationship. This proposition is now being explored in a pilot longitudinal study (Drs. D. Wells Goodrich and Donald S. Boomer, NIMH, reported at American Psychiatric Association).

Family art therapy

Pictures drawn by schizophrenics, their parents and siblings often reveal strikingly similar styles of thinking and perception, even though the patient's family exhibits no overt psychiatric symptoms.

Family art therapy is being used by NIMH researchers as a technique for exploring psychiatric difficulties and interaction patterns in families in which one member manifests an overt mental illness, particularly schizophrenia. The patient, his parents and siblings are encouraged to paint, draw, or sculpt, in sessions conducted by an art therapist. A psychiatrist or social worker, who is also engaged in conjoint psychotherapy with the same family, acts as a participant observer.

The artwork produced by the entire family often points to a severe, underlying disturbance of thought or perception, suggesting that such disturbances—overt in the patient—may be latent or hidden in other family members. Examples of thinking patterns revealed in the pictures are blurred perception of reality, fragmented thinking and highly overorganized, paranoid type of thinking.

In a detailed study of pictures of schizophrenic patients and their siblings, investigators found that although the "well" siblings' pictures seemed at first inspection to be well integrated and organized, a closer look revealed incongruities or omission of crucial details. When asked to draw a feeling or develop a picture from a casually made scribble rather than something more representational, the sibling's efforts proved disorganized, confused, fragmentary with characteristics similar to those observed in pictures drawn by schizophrenics.

Because art therapy enables family members to represent and clarify feelings that may be too deep, vague, or ambivalent for overt expression, it gives investigators an opportunity for close study of family perceptions of each other, inter-

actions and thinking patterns, and hence is a valuable research tool (Hanna Y. Kwiatkowska, Dr. Juliana Day, and Dr. Lyman C. Wynne, NIMH, in "The Schizophrenic Patient: Observations Through Family Art Therapy," Government Printing Office, 1962).

Cross-cultural studies of competence in adolescents

Students in Puerto Rico and the United States have been found to show similar responses to problem solving.

In a cross-cultural study of competence in adolescents, students in America and in Puerto Rico demonstrated similar patterns of response to problem solving, despite their different social traditions, values, and environments.

NIMH grantees at the Puerto Rico Institute of Psychiatry, Inc., successfully replicated findings of an NIMH study, conducted on American high school seniors, which identified initiative, optimism, and self-directed striving as characteristics enabling students to cope effectively with their environment.

The American study focused on three groups of college freshmen: one chosen for superior academic, social, and extracurricular abilities, one selected for high ranking on an academic achievement test, and one group of emotionally disturbed students. Each group was given the student TAT, a new psychological test in which subjects are shown slides depicting ambiguous college situations and asked to create stories about each picture. Investigators found that both normal groups differed significantly from the clinically disturbed group in active self-direction and initiative, optimism, and the ability to manage stress and keep anxiety within tolerable limits.

Similar selection criteria, test, and interview methods were used in the study in Puerto Rico. As in the American student TAT study, three comparable groups of Puerto Rican students were shown slides of college situations under standardized testing conditions and asked to compose a story about what was happening and what the outcome would be.

Results in Puerto Rico substantially paralleled the American findings. The rank order of the Puerto Rican students' scores was the same as in the U.S. study; and, in both cases, scores of the group chosen for high rank on the achievement test were considerably closer to the "competent" group than to the emotionally disturbed group.

The successful replication of the study in a different cultural setting suggests that it is possible to identify students who will be successful in mastering their environment, despite cultural differences. However, these findings do not rule out the possibility that there are important differences in the cultural structuring of adolescent competence in the two societies (NIMH Grantees Drs. P. B. Field and E. D. Maldonado-Sierra, Puerto Rico Institute of Psychiatry, Inc., and Dr. George V. Coelho, NIMH in press, *Journal of Perceptual and Motor Skills*).

Influence of parental attitudes on social deviancy

Deviant social behavior in preadolescent boys tends to develop in family settings of punitiveness, restrictiveness, and parental ambivalence coupled with low maternal self-esteem, according to an NIMH study.

Groups of fourth-, fifth-, and sixth-grade boys were rated by their classmates on a scale indicating aggression, dependency, withdrawal, depression, and likeability. These ratings were then compared with data gathered from their parents about family relationships and child-rearing practices.

The findings suggest that boys who experience relatively intense frustration in their interactions with parents will come to exhibit with considerable intensity such maladaptive behaviors as hostile aggression, overdemanding and inappropriate bids for attention, withdrawal from friendly interaction with peers, and manifestations of sadness or distress.

Interestingly, aggression seemed to be associated with fathers who had stereotyped sex role expectations and who evidenced more affection toward their sons and more use of rewards and punishment. Dependency seemed to be related to maternal rejection and sex anxiety, along with low paternal self-esteem, suggesting that dependency may develop where the father is less confident and assertive and the mother reacts to the child's expression of impulse with anxious concern or aversion.

Parents of the boys who scored high on likeability were found to be neither aggressive nor punitive and to have low demands for aggression. The mothers generally seemed satisfied with themselves and their relationships with other family members, while the fathers expressed high regard for their sons and

evaluated them as competent (NIMH Grantees C. L. Winder and Lucy Rau, Stanford University, reported in *Journal of Abnormal and Social Psychology*).

Predictions of mental disorders on basis of parental styles of thinking

Parental styles of thinking and personality functioning may be crucial determinants of some enduring patterns of behavior in their children according to a recent study.

Three groups of parents were studied by NIMH investigators: Those who had autistic schizophrenic children, those who had neurotic children, and those whose children showed overt evidences of schizophrenia in late adolescence or young adulthood. The research involved an attempt to make "blind" differentiations of the disorders on the basis of parental tests designed to measure the parents' patterns of thinking and relating.

Results showed that 24 of the 30 children were correctly identified as either schizophrenic or neurotic on the basis of parental tests, with 12 out of 15 in both the schizophrenic and neurotic groups correctly placed. Further, in studying parents of neurotic children, 13 of the 17 sets of parents studied were correctly labeled as to whether their child had an acting-out aggressive problem or a withdrawn problem.

Parents were also evaluated on the basis of Rorschach test data. Whereas about half of the parents of autistic children had schizophrenic Rorschach features, 95 percent of the parents of young adult schizophrenics evidenced such features. In contrast, 92 percent of the parents of acting-out children did not show such features, while parents of the withdrawn neurotic children ranked in the intermediate range of test scores.

Some general findings were that parents of schizophrenic children tended to show sadism, perplexity, and disaffiliation, attitudes that would impair the very basic relationship they might have with their child. Parents of young adult schizophrenics appeared to let relationships develop, but they tended to impair the focusing of attention and acquisition of meaning. Thus the behavior of their children appears logical in the sense that the forms of behavior seen in the patient relate to the major formal transactional patterns seen in the parents.

Investigators warn that their findings apply only to those varieties of patients and families studied and not, for example, to families of childhood schizophrenics who have neurological impairment. The study underscores the importance of considering mental disorders, including schizophrenia as it appears in childhood and in later life, as heterogeneous and the need to study links between definable varieties of individual mental disorder and definable varieties of family patterns (Drs. Lyman C. Wynne and Margaret T. Singer, NIMH, reported to American Psychiatric Association).

MENTAL RETARDATION

"Taste blindness" for bitterness as clue to mongolism

An NIMH grantee study suggests an association between the taste insensitivities of parents of mongoloid children and hyperthyroid activity which, in turn, may increase the frequency of chromosomal nondisjunction.

A study by NIMH grantees of biochemical-genetic factors of taste and their relation to salivary thyroid metabolites indicates that a high proportion of the parents of mongoloid children are insensitive to the taste of quinine and the bitter thiourea-type compounds. Of the 37 parents tested, 80 percent were insensitive quinine tasters. In 12 out of the 18 pairs of parents tested, both parents were insensitive to bitterness.

Preliminary data indicate that there is an association between these high taste thresholds on the one hand and hyperthyroid activity on the other. The investigators speculated that higher-than-normal thyroid hormone levels may increase the frequency of chromosomal nondisjunction, thus leading to the presence of an extra Vh chromosome in the egg, which is associated with the development of mongolism.

Since chromosomal nondisjunction has been found to increase in frequency with maternal age, and since mongolism occurs in 15 out of every 1,000 children born to mothers over 40 years of age (the total incidence of mongolism is 3 per 1,000 live births), the investigators believe the data to have epidemiological significance.

If the present findings are replicated and control data is obtained on the taste-sensitivities of parents of mentally retarded children who are not mon-

goloids, a means may be found, the investigators state, of combining age, quinine taste thresholds and other factors in a way that will make it possible to determine the probabilities of births of mongoloid children to women with various combinations of these characteristics. (NIMH grantees, Drs. R. Fischer, F. Griffin, S. England, and B. Pasamanick, Ohio State University Health Center. Reported in *Medicina Experimentalis* and in the *Journal of Neuropsychiatry*.)

Childhood intellectual deficit in schizophrenia

In a study by NIMH grantees, the childhood intelligence of adult schizophrenics was found to have been significantly lower than that of their peers.

A significant decline in childhood intelligence was found to occur in individuals destined to become schizophrenic adults, long before they were suspected of being potentially psychotic or prepsychotic.

This study involved 153 schizophrenic adults under 40 years of age who had attended Cleveland public schools from grades 2 through 6 and who had not been diagnosed as childhood schizophrenics. Intellectual level was measured by means of intelligence tests administered to these subjects while in the second and sixth grades. Comparison was made with a control group of 872 children from the same school system. Those children who were to become adult schizophrenics showed an average drop of about 10 IQ points between early and late childhood on both individual and group tests, a statistically significant drop. The control group showed a small, but not significant, increase during the same period.

In a subsequent study, the investigators found below-average intelligence to have been characteristic of schizophrenics in their childhood and to have remained characteristic of them with no significant further loss in intelligence as concomitant of schizophrenia.

Two alternative implications regarding schizophrenia are suggested by these findings: (1) The schizophrenic process begins early in life, appearing first as a faulty intellectual development and only later manifesting itself in open psychotic symptoms, showing the interdependency of emotional and intellectual development. (2) Individuals with below average intelligence have a limited reservoir of adaptive capacities and are, accordingly, less able to cope with the stresses of life, resulting in the development of schizophrenic traits later in life. (NIMH grantees, Drs. Ellen A. Lane, George W. Albee, and Jeannette M. Reuter, Western Reserve University. Reported to Eastern Psychological Association and American Psychological Association.)

Learning potential of the severely mentally retarded

NIMH grantees report that many severely defective individuals are capable of learning and "learning to learn." Through analysis of the types of errors made by mentally defectives in learning, the investigators find it may become possible to train such individuals in self-help habits.

The relationship of the four principal error factors generally acknowledged as operating in the formation of learning sets (using past experience with a problem to solve a similar problem), were studies in 58 institutionalized patients with IQ below 25 and 13 normal nursery schoolchildren ranging in chronological age from 2 years 7 months to 4 years 6 months. The investigators report that both groups were observed to make similar type errors but differed in the manner in which they eliminated these errors: the stimulus perseveration (the excess of consecutive errors beyond the expected number of errors following the first trial error) and position-habit (the consistent responses to either the right or left position irrespective of the particular object occupying the position, a tendency to prefer going to an accustomed place).

The normal child eliminates the stimulus perseveration errors slowly over many trials whereas the defective eliminates these errors early in training or not at all. The position-habit error was found to be the most characteristic error of the defectives' performance. In other words, knowledge of such facts, as maintaining the position of the object in the problem to be learned, can be of major assistance to the severely mentally retarded individual in learning a problem, particularly to those who show an elimination of the stimulus perseveration error.

These investigators point out that intelligence tests, indices of language skills, or general observation fail to yield information from which the learning potential of many defective individuals can be predicted. They feel that careful systematic observation of, and intensive study of error factors in, the patient's behavior might provide clues to the learning potential and lead to training pro-

cedures which would ameliorate a serious problem. (NIMH grantees, Dr. N. R. Ellis and associates, George Peabody College for Teachers and Dr. Margaret W. Pryer, State Colony and Training School, Pineville, La. Reported in the *Journal of Comparative and Physiological Psychology*.)

Underlying mechanism of phenylketonuria

NIMH grantees have demonstrated that in phenylketonuria, the brain serotonin level is lowered by an elevated serum phenylalanine level per se, rather than by its metabolites.

It has been well established that serotonin metabolism is altered in phenylketonuria, but it has not been demonstrated whether phenylalanine per se or metabolites, or both, are responsible for these changes. These investigators fed phenylalanine and its important metabolites to rats. Analyses of brain samples for serotonin after several days on these diets showed that phenylalanine feeding effectively lowered brain serotonin. Phenylpyruvic acid feeding did so less effectively, and phenylpyruvic acid and o-hydroxyphenylacetic acid feeding caused no significant change. The depressed brain serotonin levels associated with the phenylalanine diet resulted in a several-fold increase in the serum phenylalanine level but in only a very small increase in urinary phenylpyruvic acid. In contrast the diet supplemented with phenylpyruvic acid (an acid known to be readily converted to phenylalanine) caused a massive excretion of phenylpyruvic acid and a twofold to threefold increase in serum phenylalanine, but was less effective in lowering brain serotonin levels. These findings led the investigators to conclude that the brain serotonin level is lowered by an elevated serum phenylalanine level per se.

These investigators believe their findings indicate that the mechanism by which the brain serotonin level is significantly lowered by phenylalanine but not by its metabolites is best explained by the fact that transport of the precursor of serotonin, 5-hydroxytryptophan (5-HTP), into brain is inhibited by phenylalanine, as recently reported by other investigators.

Further, since the increased serum phenylalanine level was accompanied by only a slight rise in urinary phenylpyruvic acid, they suggest that, in the management of phenylketonuria, controlling the serum phenylalanine level of affected children should be accomplished more closely than by checking for urinary phenylpyruvic acid. Simple methods for determining the serum phenylalanine levels are available. (NIMH grantees, Dr. W. J. Culley and associates, Purdue University. Reported in the *Proceedings of the Society for Experimental Biology and Medicine*.)

Psychiatric outpatient services to the mentally retarded

The relative frequency of mental retardation in patients seen by outpatient psychiatric clinics has remained almost constant during a recent 5-year period.

Data for 1954-59 on outpatient psychiatric clinics in the United States, totaling about 1,400 in 1959, have been analyzed by NIMH investigators. The analysis shows that mental deficiency was present in about 30 percent of patients of preschool age, 15 percent of the school-age group and less than 4 percent of those beyond school age.

The NIMH study indicates that the proportion of patients with mental deficiency or brain syndromes is about the same for girls as for boys. However, since twice as many boys as girls are seen in clinics, mentally deficient boys outnumber girls two to one. On the other hand, a higher proportion of girls are found to be severely retarded.

An estimated 26,000 persons with mental deficiency were served by these clinics. This estimate is based on the number of patients for whom a diagnostic classification was reported; thus the total number of mental deficient served is more probably around 40,000.

Other findings demonstrate that clinics provide primarily diagnostic or evaluative services to the mentally retarded and that these patients receive relatively brief service. During the years of the study, about two-thirds were evaluated and then referred to other community agencies, with a high proportion of such referrals made to schools and welfare agencies, sources which yield most of the original referrals to the clinics.

Researchers point out that while the educable and rehabilitative function in most communities seems to lie with the educator, it is not clear which agency should provide services and guidance for preschool children and for the families of defective and organically handicapped children of all ages.

The special diagnostic and treatment services, along with the complex of community services, required by such children suggests that no one agency can meet their needs adequately. As a consequence, investigators urge that mental health clinics intensify efforts to coordinate their services with those of other agencies to provide more complete programs for the retarded.

The higher rate for boys with organic or nonorganically based mental deficiency indicates a need for intensive research into causes of this sex difference. (Drs. Anita K. Bahn and Caroline Chandler, and Vivian B. Norman, NIMH. Reported in *American Journal of Mental Deficiency*.)

ALCOHOLISM

A county health department approach to alcoholism

Rehabilitation of alcoholics as part of an overall county public health program is underway in Prince Georges County, Md., through a 4-year cooperative program sponsored by the county health department and the Mental Health Study Center, NIMH.

Established through a NIMH grant in 1959, the program combines clinical treatment of patients and their families with community activities in alcoholic rehabilitation.

By placing the program within the physical and administrative framework of the county health department, it has been possible to make advantageous use of the department's resources and personnel. The department has provided home visits to alcoholics, drugs, dental services and help in the preparation of educational materials, along with well-developed procedures for data gathering and research.

Followup outpatient care is facilitated by visits of a staff psychiatrist from the alcoholism clinic to patients at the Prince Georges General Hospital and by notification from the Spring Grove State Mental Hospital when patients are released.

Referrals to the clinic from relatives are as frequent as self-referrals, underscoring the emphasis on the family aspect of alcoholism. Other patients come to the program through professional sources in the community, such as physicians, clergy, and social agencies.

The staff psychiatrist at the alcoholism clinic refers patients to the Prince Georges General Hospital when hospitalization is indicated. He also sees all alcoholic patients at the general hospital, and this has resulted in a marked facilitation of followup care. Patients hospitalized for alcoholism at the Spring Grove State Mental Hospital are notified of the clinic services before their discharge, as well as the hospital notifying the alcoholism clinic when the patient is to be released. (Dr. Bertram S. Brown, NIMH, and Drs. Augusto Esquibel, Murray Grant, and Edward Pickford, Prince Georges County Health Department. Reported in *Public Health Reports*.)

Encouraging the alcoholic to follow through with treatment

NIMH grantees have found initial hospital treatment is a major factor in determining whether alcoholics return for followup care.

Special care and attention from well-prepared hospital emergency ward personnel can mean the difference between those alcoholic admissions who subsequently seek outpatient treatment and those who do not, according to a research study partially supported by an NIMH project grant.

In the year-long study of 200 alcoholics admitted to the emergency ward of the Massachusetts General Hospital, half received special treatment as the experimental group, and half, the control group, received routine hospital care. Results showed that 65 percent of the experimental group subsequently made initial visits to the hospital's outpatient alcoholism clinic, in contrast to 5 percent of the control group; 42 percent of the experimental group made five or more visits, compared with only 1 percent of the control group.

Upon admission to the hospital, patients in the experimental group were assigned to a clinical treatment team, consisting of a psychiatrist and a psychiatric social worker. The team constituted the alcoholic's initial contact with the hospital and worked closely with him during his stay, concentrating upon meeting his excessive dependency needs, bolstering his low self-esteem and low tolerance for frustration, on the theory that neglect of these special needs of the alcoholic would discourage him from seeking further treatment as an outpatient.

Continuity of care was emphasized: the patient learned that the psychiatrist was "his doctor," the social worker "his social worker." The treatment team

expressed its interest in the alcoholic as a human being by taking direct action to help him solve his social problems—getting him a place to stay, a meal, and the like.

The high incidence of clinic visits by patients who received such special treatment is particularly significant when viewed in connection with a previous study at the same hospital, which showed that of 1,200 alcoholic admissions in a given year, less than 1 percent subsequently sought treatment at the outpatient clinic, although such treatment was readily available to them.

Both experimental and control groups were composed of men generally considered alienated from society and unreachable by traditional clinical methods. They had a high rate of unemployment and records of frequent arrests; many were homeless or poverty-stricken and few had stable marital relationships. Yet two-thirds of those receiving special treatment responded by seeking further care as outpatients and well over one-third made five or more clinic visits, strongly indicating that even alienated groups can be reached by special methods utilizing their initial hospital contact. (NIMH grantees Dr. Morris E. Chafetz and associates, Massachusetts General Hospital. Reported in the *Journal of Nervous and Mental Disease*.)

DRUG ADDICTION

A followup study of discharged drug addicts

The treated drug addict who returns to his community remains a generally antisocial individual with a high rate of readdiction, arrest, and unemployment, according to a 5-year NIMH followup study of hospitalized narcotic drug addicts.

The study, covering a sample group of 453 of an original 1,359 patients discharged from the U.S. Public Health Service hospital in Lexington, Ky., was conducted by a field team from the New York Demonstration Center, Research Utilization Branch, NIMH.

More than 97 percent of the sample group became readdicted at some time during the 5 years after treatment. However, by the fifth year after discharge only an estimated 46 percent were readdicted, while 49 percent were abstinent, either voluntarily or involuntarily, through forced disuse of drugs due to incarceration in hospitals or penal institutions.

Age seemed to be significant in voluntary abstinence. The over-30 age group showed a significantly higher voluntary abstinence rate and a greater ability to remain drug free, compared with the under-30 group. Generally, abstinence increased with passage of time while rate of readdiction decreased. Of the total sample, an estimated 42 percent was voluntarily abstinent at some time during the study period.

Antisocial data collected showed that approximately 70 percent had one or more arrests, with the under-30 group evidencing the higher arrest rates. Two-thirds of the reported arrests involved definite narcotic violations, while almost all of the remaining violations were illegal acts undertaken to support the addiction. These findings appear to support the theory that it is the influence of narcotics which makes the criminal, rather than the criminal which makes the addict. There were no differences in arrest rates between those who were voluntarily abstinent at some time and the chronically readdicted, though in the former group almost all arrests occurred at times of addiction.

About 41 percent of the sample group were unemployed 5 years after discharge. However, patients who had experienced some periods of voluntary abstinence showed an unemployment rate of only 30 percent and of this group, some 59 percent were employed full time; by contrast, chronically addicted discharges showed a full-time employment rate of only 13 percent.

Fewer than 10 percent of the discharges received psychiatric care within the followup period and the outpatient clinical type of care was particularly infrequent.

The study suggests the need for a systematic program of community aftercare and/or supervision for treated drug addicts in view of their high rates of relapse and antisocial behavior. (Henrietta J. Duvall, Ben Z. Locke, and Leon Brill, NIMH. In press, *Public Health Reports*.)

Social deviance in alcoholics, addicts and criminals

A study of personality traits of alcoholics, narcotic addicts and criminals indicates that social deviance is the only characteristic common to all three.

NIMH investigators studied groups of institutionalized alcoholics, addicts, and criminals, using the Minnesota Multiphasic Personality Inventory (MMPI) as an instrument for measuring personality configurations. Except for behavior pecu-

liar to the particular activity, no personality traits appeared to be associated specifically with either alcoholism, addiction, or criminality.

Analysis of the data showed that the three groups could not be differentiated from each other in terms of personality characteristics, except for minor differences. Similarities among the groups with respect to specific measures of social deviance far exceeded the dissimilarities. Of the minor differences which appeared, the only one of statistical significance was depression, with both addicts and alcoholics ranking higher on this scale than the criminals.

Investigators conclude that if alcoholics, addicts, and criminals cannot be differentiated on the basis of personality characteristics, specific causal factors for these types of behavior must be sought elsewhere. Social deviance was found to be a general predictor of the various types of behavior studied but was not predictive of specific asocial, unsocial or antisocial actions. (Drs. Harris E. Hill and Charles A. Haertzen, NIMH Addiction Research Center, and Dr. Howard Davis, Minnesota State Department of Public Welfare. Reported in *Quarterly Journal of Studies on Alcohol*.)

EPIDEMIOLOGICAL STUDIES

Epidemiology of mental disorders in a metropolitan population

Findings have been reported in an NIMH-supported 8-year study designed to measure the total prevalence of all degrees of mental disturbance, from mild to extreme in an urban population, and the prevalence of cases under treatment for mental illness.

The study, conducted by an interdisciplinary research team in a 190-block residential area in midtown Manhattan, revealed that, of a random sample—1,660 of 170,000 persons—of adults between 20 and 59 years of age, 10.8 percent were classified as having symptoms indicating the presence of extreme or serious mental disturbance. An additional 13.1 percent were classified as having marked mental disturbance. Only 18.5 percent were classified as being without some degree of mental disturbance.

The sample was psychiatrically screened in single 2-hour long interviews based on a questionnaire of about 400 items. The 110 questions on mental health were adapted in part from items in the Army's neuropsychiatric adjunct and the Minnesota multiphasic inventory. Two psychiatrists made independent evaluations of each respondent on the basis of material obtained in the interview. The report indicated they were able to concur in their evaluations of the degree of mental disturbance in most cases. The term "mental disturbance" as used in this study, is descriptive rather than diagnostic, and the extent of disturbance is measured in functional and behavioral terms.

A 1-day patient census, or enumeration of prevalence, was made of all persons resident in the area from which the sample was taken—regardless of age—under treatment for mental illness on May 1, 1953, by private psychiatrists and clinical psychologists, outpatient clinics, State and Veterans' Administration hospitals, and licensed private mental hospitals of New York and other States. A total of 2,470 residents were found to be under treatment at the time the patient census was taken.

Data from both the patient census and the sample survey confirm the findings of an earlier study conducted in New Haven that there is a positive correlation between socioeconomic status and the amount of psychiatric treatment received. As one moves down from the higher socioeconomic levels to the lower socioeconomic levels, the rates of mental morbidity increase and rates of treated mental morbidity decrease. (Leo Srole, Marvin K. Opler, and Thomas C. Langner in *Mental Health in the Metropolis*, vol. I, McGraw-Hill Publishing Co., 1962.)

WEDNESDAY, MARCH 13, 1963.

NATIONAL HEART INSTITUTE

WITNESSES

DR. RALPH E. KNUTTI, DIRECTOR, NATIONAL HEART INSTITUTE
 DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF
 HEALTH

E. H. HENSCHER, EXECUTIVE OFFICER, NATIONAL HEART INSTITUTE

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL
 INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	3,933	4,601	4,844
Positions other than permanent.....	70	76	80
Other personnel compensation.....	43	34	77
Total personnel compensation.....	4,046	4,711	5,001
12 Personnel benefits.....	489	529	580
21 Travel and transportation of persons.....	223	294	319
22 Transportation of things.....	60	45	47
23 Rent, communications, and utilities.....	106	113	126
24 Printing and reproduction.....	25	34	34
25 Other services.....	819	1,460	1,231
Payment to National Institutes of Health management fund.....	5,107	6,031	6,265
26 Supplies and materials.....	786	798	813
31 Equipment.....	622	441	463
32 Lands and structures.....		565	435
41 Grants, subsidies, and contributions.....	78,733	102,611	113,761
Subtotal.....	91,019	117,632	134,075
Deduct quarters and subsistence charges.....	15	16	16
Total obligations.....	91,003	117,616	134,059

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	634	755	762
Full-time equivalent of other positions.....	12	15	21
Average number of all employees.....	577	643	682
Number of employees at end of year.....	632	729	753
Average GS grade.....	7.1	7.4	7.4
Average GS salary.....	\$6,388	\$6,959	\$6,974

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	63,031	82,661	97,183
(b) Fellowships.....	4,406	5,950	6,399
(c) Training.....	11,296	14,000	15,179
Total, grants.....	78,733	102,611	118,761
2. Direct operations:			
(a) Research.....	8,898	10,483	10,608
(b) Collaborative studies.....	759	1,323	1,426
(c) Training activities.....	185	200	250
(d) Review and approval of grants.....	1,437	1,904	2,183
(e) Program direction.....	408	530	396
(f) Gerontology building.....		565	435
Total, direct operations.....	11,687	15,005	15,298
Total program costs, funded ¹	90,420	117,616	134,059
Change in selected resources ²	583		
Total obligations.....	91,003	117,616	134,059
Financing:			
Comparative transfers to other accounts.....	19,846	18,124	
Unobligated balance brought forward (-).....		-1,000	-435
Unobligated balance carried forward.....	1,000	435	
Unobligated balance lapsing.....	21,013	12,177	
New obligational authority.....	132,862	147,352	133,624
New obligational authority:			
Appropriation.....	132,912	147,398	133,624
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (-).....	-50	-46	
Appropriation (adjusted).....	132,862	147,352	133,624

¹ Includes capital outlay as follows: 1962, \$315,000; 1963, \$441,000; 1964, \$463,000.

² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$248,000 (1962 adjustments, \$2,020,000); 1962, \$2,851,000; 1963, \$2,851,000; 1964, \$2,851,000.

GENERAL STATEMENT

Mr. FOGARTY. Dr. Knutti, we will take up the budget request for the Heart Institute now.

Dr. KNUTTI. Mr. Chairman, with your permission, and if there is sufficient time, I would like to expand a little bit on my very short prepared summary statement.

Mr. FOGARTY. We will place your detailed statement in the record, and you may take as much time as you wish with your oral statement. (The prepared statement referred to follows:)

Mr. Chairman and members of the committee, during the past year, many new heart research findings—some quite dramatic—have been reported. There have also been substantial accomplishments in other areas of Heart Institute work, and new activities have been established to strengthen the research attack against the Nation's No. 1 killer.

However, the total figure climbs steadily higher. In 1962 an estimated total of 947,210 people died from diseases of the heart and circulatory system, an increase of nearly 26,000 over the previous year.

This statement is a brief review of the institute's 1962 program activities and research accomplishments. It is hoped that it will be of value to the Congress as it weighs the progress of current programs and the merits of future activities. This statement does not discuss the heart disease control program, since funds for that purpose are requested in the budget of the Bureau of State Services.

In the course of considering the specific activities of a program, research or otherwise, it is quite possible to lose sight of the overall problem, the staggering effect the disease has upon the health and economy of the Nation. A few facts and figures on heart disease are, therefore, in order as a means of realistically viewing the horizons which lie ahead for the programs of the National Heart Institute.

HEART DISEASE: FACTS AND FIGURES

Diseases of the cardiovascular system took an estimated 947,210 lives in 1962—well over half of all the deaths that occurred in the United States during the year—and an increase of nearly 26,000 over 1961.

Although detailed breakdowns of the estimated 1962 toll are not yet available, figures for 1961 show that the cardiovascular diseases exacting the greatest tolls were arteriosclerotic heart disease, which includes coronary disease or "heart attacks" (502,351 deaths); vascular lesions affecting the brain, such as "strokes" (192,951); and hypertension, with or without accompanying heart disease (75,467 deaths).

Cardiovascular disease strikes heavily among the young and middle aged, as well as those in the older ages. Over 25 percent of all deaths in the age group 25 through 44, and 50 percent of those in the age group 45 through 64, are caused by heart and blood vessel diseases.

In the past decade, the number of deaths from cardiovascular disease increased from 776,114 in 1952 to 924,622 in 1961. This rise has resulted largely from the general aging of the population and the upward trend in mortality from arteriosclerotic heart disease, the death rate for which has increased 22 percent from 226 per 100,000 population in 1952 to 275 in 1961.

The death rate for strokes and other vascular lesions affecting the brain has remained about the same, as has that for general arteriosclerosis. Three cardiovascular categories have, however, shown definite declines in the 1952-61 period. They are rheumatic fever and chronic rheumatic heart disease—28 percent decrease; nonrheumatic chronic endocarditis and other myocardial degeneration—38 percent decrease; and hypertension, with or without heart involvement—33 percent decrease.

RESEARCH ACCOMPLISHMENTS

Research conducted by NHI scientists and grantees during the year has resulted in substantial contributions to the store of knowledge concerning the cardiovascular system and its functions in health and disease. It has also resulted in improved methods of diagnosis, treatment, and prevention of certain cardiovascular disorders.

Among the hundreds of research findings reported last year were the results of studies showing that—

Desmosterol, formerly thought to be the immediate precursor of cholesterol, is only one of many possible sterol precursors; and, in the general scheme of cholesterol synthesis, may be of only minor importance.

Both norepinephrine and adrenocortical hormones are needed to mobilize stored metabolic fuels to meet the body's energy demands during periods of fasting, exercise, or stress.

Alpha-methyl DOPA (Aldomet, Merck Sharp & Dohme), a drug which strikes at the mechanisms maintaining norepinephrine stores at sympathetic nerve terminals, has recently passed through experimental stages to use by physicians and appears to be highly effective against hypertension, including the malignant phase of the disease.

Certain monoamine oxidase (MAO) inhibitors reduce blood pressure by preventing the release of norepinephrine at sympathetic terminals, thus halting vasoconstrictive nerve messages short of the blood vessel wall.

The production of norepinephrine and epinephrine, amines strongly suspected of playing some role in hypertension, can be blocked by a new family of drugs which inhibit the enzyme dopamine-beta-oxidase.

The heart can "recharge" its sympathetic terminals by taking up norepinephrine from the circulation or by synthesizing this amine from the amino acid tyrosine.

Digitalis and related cardiac stimulants increase the vigor of contraction both in normal and in failing hearts.

Angiotensin does not increase the contractility of the heart, but increases the resistance against which the heart must work; hence the drug should not be used in the treatment of congestive failure.

Xylocaine, a widely used local anaesthetic, is clearly superior to procaine amide for treating ventricular fibrillation, a dreaded complication of cardiac surgery.

Cholesterol and epinephrine, together or separately, can produce an inflammatory reaction within the walls of large blood vessels which could possibly promote the development of atherosclerotic lesions.

Diets containing foods modified as to their fats can be made tasty, simple to follow, and highly effective in reducing serum cholesterol levels.

The liver enzyme, hepatocatalase, effectively inhibits cholesterol synthesis in laboratory animals without interfering with the production of essential metabolites and without producing toxic side effects.

Sedentary workers had three times as many heart attacks during a 10-year period as did manual laborers from the same controlled population.

Elevated hematocrit (a major determinant of blood viscosity) significantly increases the risk of heart attacks.

When pregnant rats are subjected to various diets or are treated with certain hormones or drugs, their young develop a form of hypertension closely resembling essential hypertension in man.

Infusions of the drug mannitol protect the patient during open-heart surgery by reducing damage done to red blood cells by the heart-lung machine.

A 5-percent glucose solution, used to prime the heart-lung machine in lieu of homologous heparinized blood, reduces the kidney depression that sometimes follows use of heart-lung machines during open-heart surgery.

HEART INSTITUTE RESEARCH

The research conducted by the National Heart Institute places major emphasis upon basic cardiovascular investigations. These studies seek new knowledge about the structure, function, and abnormalities of the cardiovascular system. Closely associated with these studies are those concerned with the application of fundamental knowledge to the diagnosis, prevention, and treatment of diseases of the heart and blood vessels. Some Heart Institute research in these areas is described below.

Cholesterol.—There is a formidable body of statistical evidence that elevated serum cholesterol levels greatly increase the risk of developing atherosclerosis. Frequently, elevated serum cholesterol levels can be traced directly to the diet, and corrected by reducing its total fat calories and substituting vegetable or marine oils, high in unsaturated fats, for animal fats high in cholesterol and saturated fats.

Such dietary measures are very often successful in controlling serum cholesterol levels, and they need not produce any major upheaval in habitual dietary patterns. However, many cases of hypercholesterolemia do not respond to such diets, largely because the liver can manufacture cholesterol from any item in the diet from soup to nuts. Thus the search continues for drugs that can reduce serum cholesterol levels by inhibiting the synthesis of cholesterol by the liver.

But much more must be learned about the metabolism of cholesterol and the compounds used in its production before the blockade of cholesterol synthesis can be attempted with any assurance that this blockade will do more good than harm.

NHI studies conducted this year have been concerned with the steps involved in cholesterol synthesis once the basic sterol nucleus has been laid down. In these studies, Triparanol (Merrell), a drug that blocks cholesterol synthesis, has proved to be a valuable research tool.

When cholesterol synthesis is blocked with this drug, the fall in blood and tissue concentrations of cholesterol is accompanied by increased concentrations of desmosterol, a compound identical to cholesterol except for two missing hydrogen atoms in the sterol side chain. Thus it appeared that desmosterol was the immediate precursor of cholesterol.

Subsequent studies have shown that desmosterol is only one of many possible sterol precursors of cholesterol, and, in the general scheme of cholesterol synthesis, may be of minor importance. It appears that the enzyme responsible for adding two hydrogen atoms to desmosterol is not highly specific in its action. It performs the same function for a number of other sterols which can be used in the synthesis of cholesterol. Although desmosterol is the major sterol ac-

cumulating in tissues when this enzyme activity is inhibited, there are also increases in the tissue concentrations of a number of other sterols with unsaturated side chains and decreases in the concentrations of sterols with saturated side chains.

Fatty acids.—Adipose tissue provides a major reserve depot for metabolic fuels needed to sustain the organism during periods of fasting, increased physical activity, or stress. Under such circumstances, the triglycerides (neutral fat) stored in this tissue can be broken down and their free fatty acids (FFA) released into the circulation to meet current energy demands.

NHI studies indicate that two keys are needed to unlock these energy reserves. One is provided by the adrenal cortex, the other by the sympathetic nervous system. If either key is lost, the animal can draw only on those metabolic fuels already present in his blood. As this supply dwindles, it cannot be replenished from his fuel reserves. When it is gone, so is he.

Thus, if an animal is deprived of his adrenal cortex and is subsequently exposed to cold or forced to perform muscular exercise, his body temperature falls rapidly and he dies within a few hours. These dire consequences are prevented if he is treated with any of several adrenocortical hormones; but norepinephrine or epinephrine, normally potent FFA mobilizing agents, have no such protective effect.

If the animal's adrenal cortex is left intact, but his sympathetic nervous system is knocked out with drugs, he also succumbs rapidly when subjected to cold or exercise. This can be prevented by treating him with norepinephrine or epinephrine, but not by treatment with adrenocortical hormones.

In the mobilization of FFA, norepinephrine, the chemical messenger of the sympathetic nervous system, is released directly into adipose tissue by sympathetic nerve discharges. Norepinephrine stimulates FFA release by stepping up the activity of lipases: enzymes which break down triglycerides. However, norepinephrine appears to be unable to activate these enzymes unless adrenocortical hormones are also present.

Other NHI studies have assessed the effects of FFA concentrations upon the metabolic rate of liver, muscle, and other tissues. The findings indicate that it may be possible to "force feed" the cellular furnaces with metabolic fuels. Tissues exposed to elevated FFA concentrations took up and burned more FFA, presumably just because it was there. These findings suggest that the elevated basal metabolic rate characteristic of hyperthyroidism might be secondary to the abnormally high rate of FFA mobilization accompanying this disorder. Recent studies have shown that hexamethonium, a drug that inhibits FFA release from adipose tissue, also reduces basal metabolic rate in hyperthyroid subjects.

Lipoproteins.—Lipoproteins are large fat-protein molecular complexes that carry about 95 percent of the lipids found in serum. They are divided into two weight classes: high-density and low-density lipoproteins. Although the distribution of serum lipids between these lipoprotein classes appears to be a factor determining relative susceptibility to atherosclerosis, the precise roles played by the two classes in human fat metabolism have remained obscure.

Currently under study by NHI scientists is a disorder of lipid storage that may help to clarify these roles. Tangier disease is characterized by the accumulation of large quantities of cholesterol in tonsils, liver, spleen, and other reticuloendothelial tissues, and by a virtual absence of serum high-density lipoproteins. Thus, the four cases of Tangier disease discovered so far provide unique opportunities to study the role of lipoproteins in the metabolism of lipids, especially cholesterol. The clinical manifestations of the disorder indicate that the high-density fraction may play some essential role in the handling of cholesterol by the body, and current studies are seeking to discover just what that role might be.

Tangier disease also appears to be genetically determined, and thus provides opportunities to study genetic factors operating in the synthesis of high-density lipoproteins.

Hypertension.—Many recent advances in the drug treatment of hypertension have stemmed primarily from increased scientific knowledge about the metabolism of amines. These are nitrogen-containing compounds made by the body from the amino acids of dietary protein. Several are powerful stimulants that increase heart rate, heart output, and blood pressure. Two of them—the catechol amines norepinephrine and epinephrine—have long been suspected of playing some nefarious role in hypertension, but neither they nor any of their chemical relatives have ever been convicted.

Nevertheless, many drugs currently used against hypertension appear to owe their effects on blood pressure to their effects on amine metabolism. The amine figuring most prominently in the action of these drugs is norepinephrine. Norepinephrine, a chemical transmitter stored at most sympathetic nerve terminals, is liberated by sympathetic nerve impulses to convey their messages to target organs. Among these targets are the muscles in the walls of blood vessels. Drugs which interrupt this chemical messenger service can prevent blood vessel constriction by halting vasoconstrictive messages short of their targets.

One such drug, α -methyl DOPA (Aldomet, Merck, Sharp & Dohme), strikes at the mechanisms which maintain norepinephrine stores at sympathetic terminals. The norepinephrine normally held in reserve there is turned loose to be set upon and destroyed by enzymes. Eventually too little is left to handle sympathetic nerve traffic.

α -methyl DOPA has continued to perform impressively against hypertension, including the malignant phase of the disease, in long-term clinical studies at NHI. It is a powerful hypotensive agent, especially when used in conjunction with thiazide diuretics. Its smoothness of action, relative freedom from adverse side effects, and mild tranquilizing properties make α -methyl DOPA the drug of choice for many hypertensive patients. The drug has recently been placed on the market for use by physicians.

Another blood pressure drug undergoing clinical trials at NHI is MO-911 (Abbott). This drug belongs to a family of compounds called monoamine oxidase inhibitors. These block the action of an enzyme largely responsible for inactivating norepinephrine, epinephrine, and a number of other amines. Several MAO inhibitors are powerful hypotensive agents. Although nobody could explain why slowing the destruction of such powerful stimulants as norepinephrine should lower blood pressure, there appeared to be a direct relationship between the potency of these drugs as MAO inhibitors and their potency as hypotensive agents.

Recent NHI studies may have provided the answer to this riddle. Their findings indicate that certain MAO inhibitors may block sympathetic transmission by preventing the release of norepinephrine at sympathetic terminals. This heretofore unsuspected action of MAO inhibitors provides a plausible explanation for the blood pressure effects of certain of these drugs.

Since norepinephrine and epinephrine are the amines most strongly suspected of playing some role in hypertension, many scientists feel that drugs able to block the synthesis of these amines would provide a promising new approach to the treatment of the disease.

A family of compounds called decarboxylase inhibitors appear to do just that. These compounds inhibit an enzyme whose action is essential to the production of norepinephrine, epinephrine, and other amines. However, though certain of these compounds were highly effective in the test tube, none was able to make any appreciable dent in amine production in vivo. It now appears that the tissues are so well endowed with decarboxylating enzymes that significant activity persists even when decarboxylase inhibition approaches 100 percent.

NHI scientists are currently evaluating still another family of enzyme inhibitors. These act on dopamine-beta-oxidase, an enzyme that acts one step further along the norepinephrine-epinephrine assembly line than does decarboxylase. Since the tissues are not nearly so well equipped with dopamine-beta-oxidase as with decarboxylase, an effective inhibitor can seriously curtail their catechol amine production. Further, dopamine-beta-oxidase blockade does not interfere with the production of serotonin, tryptamine, and other amines of biologic importance.

Several of these inhibitors have been found to block catechol amine synthesis in laboratory animals. The consequences of that blockade are still to be evaluated. The present group of inhibitors are far too toxic to merit serious consideration as potential therapeutic agents. However, these drugs should provide useful tools for determining whether the blockade of catechol amine synthesis is likely to offer a sound approach to hypertension therapy.

Congestive heart failure.—When the heart is taxed with excessive circulatory burdens by hypertension or other factors, a number of mechanisms help the heart to meet its circulatory obligations by increasing its pumping efficiency. If the demands imposed upon the heart become exorbitant, even these compensatory mechanisms may not be enough, and the heart goes into failure.

One of the most important of these compensatory mechanisms is provided by the sympathetic nervous system. Sympathetic nerve discharges release norepinephrine in the heart. This amine augments heart output by increasing heart rate and also the vigor of heart muscle contraction. NHI studies indicate that the heart may keep its sympathetic nerve terminals fully charged with norepinephrine by either of two mechanisms. The heart readily takes up and stores norepinephrine from the circulation; it also has all of the enzymatic machinery needed to synthesize norepinephrine from the amino acid tyrosine.

The important role of the sympathetic nervous system in providing support to the failing heart was demonstrated in two clinical studies by NHI scientists. In the first, the scientists compared sympathetic activity during exercise in normal subjects with that in patients with congestive heart failure. In every instance, sympathetic activity was significantly higher in the patients.

In the second study, they administered guanethidine, a blood pressure lowering drug that inhibits sympathetic activity, to 10 patients with borderline congestive heart failure. The drug clearly increased the symptoms of heart failure in 5 of the 10. Because many patients with congestive failure are also hypertensive, this finding underscores the need for extreme caution when using such drugs in patients with limited cardiac reserve.

When the body's own compensatory mechanisms prove inadequate to keep the heart from lapsing into failure, digitalis, and related cardiac stimulants are commonly used to augment heart output. Because these drugs do not increase heart output in normal subjects, scientists have questioned whether they have any effect on the normal heart.

NHI studies have shown that these drugs do increase the vigor of contraction in normal as well as in failing hearts. In normal subjects, heart output does not increase because the drugs also cause the peripheral blood vessel to constrict. As a result, the gain in heart contractility is largely offset by the increased resistance against which the heart must work. In patients with congestive heart failure, however, these drugs increase heart contractility while decreasing peripheral resistance. The reason for these strikingly different effects is not clear.

Another compound that has been reported to be a cardiac stimulant possibly useful in the treatment of congestive heart failure is angiotensin. Angiotensin, a powerful blood vessel constrictor, is produced in the body through the interaction of renin (a hormone from the kidney) with a plasma protein. The effects of angiotensin on blood pressure have been intensively studied, but considerably less is known concerning its effects on the heart itself.

NHI studies, assessing the action of angiotensin on the heart, raise some doubts concerning the use of angiotensin in cases of congestive heart failure. The drug has little direct effect upon the heart, and that is to decrease its contractility somewhat. The drug caused an immediate sharp rise in blood pressure, thus increasing the resistance against which the heart was working. However, heart rate and contractility did not increase until later. These later effects appeared to result from sympathetic stimuli, possibly arising from peripheral receptors.

Although the autonomic nervous system and a number of other extrinsic mechanisms operate to adjust heart performance in accordance with current circulatory demands, NHI studies indicate that the heart is also capable of a striking degree of autoregulation.

Even in the absence of extrinsic control mechanisms, the heart can adjust its performance to maintain its output per pumping stroke even if heart rate and blood pressure are varied over a fairly wide range.

When heart rate is increased, other factors being held constant, the heart continues to perform the same amount of work with each pumping stroke even though less time is available to do it. The heart modifies the timing of each event in the cardiac cycle so as to compensate precisely for the shorter time interval between pumping strokes.

If aortic blood pressure is raised, other factors being held constant, the heart will modify its contractility so as to eject the same amount of blood with each pumping stroke, even though it is now working against a higher resistance.

NHI scientists are currently seeking the intrinsic mechanisms underlying this autoregulatory activity.

Surgery.—An important segment of NHI research in cardiovascular surgery deals with the design, construction, and evaluation of artificial heart valves. Of great importance in determining the ultimate success or failure of such a

valve are the materials used in its construction. These materials must neither affect nor be affected by body fluids or tissue; must retain their strength and elasticity over years of constant hard use; must not promote the formation of clots; and must be porous enough to allow the ingrowth of host tissue, which is essential to firm healing.

In some cases this tissue ingrowth can also pose problems. If the material used in the construction of valve leaflets is too porous, excessive ingrowth of fibrous tissues may make the leaflet too stiff to open and close properly. In investigations to determine how large the pores of such material should be for optimum performance, NHI scientists are working with a material composed of alternating fibers of dacron and collagen. The pores of this material, initially very small, gradually become larger as the collagen, a normal protein constituent of the body, is slowly absorbed.

Other research has been concerned with physiological factors underlying certain of the complications that may arise during cardiovascular surgery and with the evaluation of drugs and procedures for coping with such surgical emergencies.

A serious complication of heart surgery is ventricular fibrillation, the uncoordinated contraction of the heart muscle resulting from derangements in the activity of its specialized conducting system. Although procaine amide is widely used to counter ventricular fibrillation, NHI studies suggest that the drug may do more harm than good. In addition to depressing heart output and blood pressure, the drug lowers the electrical threshold of the heart, rendering it more sensitive to the very factors initially responsible for the fibrillation.

However, xylocaine, widely used as a local anesthetic, increases the electrical "tolerance" of the heart without adverse effects on heart contractility or blood pressure. The NHI scientists conclude that it should be the drug of choice in such situations.

Another dreaded complication of heart surgery, cardiac arrest, may occur, not during the operation itself, but during the induction of anesthesia. An inadequate supply of oxygen to the heart (cardiac hypoxia) is generally blamed for such instances. However NHI scientists have found that the major cause stems from systemic hypoxia, which triggers nervous reflexes that can slow the heart or stop it completely even if the heart's own oxygen supply is adequate. The heart itself is little affected by moderate hypoxia, provided that the systemic oxygen supply is adequate.

RESEARCH GRANTS

The research grants program of the National Heart Institute supports heart disease research in over 300 universities and hospitals throughout the Nation and abroad. More than 2,000 separate research projects are underway. The following summaries represent only a few of the hundreds of findings reported in the scientific literature during the past year.

Atherosclerosis.—The circumstantial evidence linking elevated serum cholesterol levels to the development of atherosclerotic lesions has spurred research seeking safe, effective ways of bringing serum cholesterol levels down to normal.

One approach has been to reduce cholesterol intake by limiting the amount of animal fat in the diet. This approach has enjoyed only limited success, however, since cholesterol can be synthesized within the body from other materials. On the other hand, diets in which saturated fats have been largely replaced by unsaturated fats have usually been effective. This raises the question of whether such diets can be made tasty enough so that patients will stick to them for long periods of time.

Encouraging results were reported by NHI grantees, who placed 25 young married couples on a diet consisting of a wide variety of commercially prepared foods, modified as to the quantity and nature of fats they contain, for a 10-month period. The altered foods were low in saturated fat, with polyunsaturated oils replacing the deleted fats in many cases. In a few instances, fatty foods which could not be modified were eliminated. The investigators report that greatly lowered serum cholesterol levels can be obtained with suitably modified, palatable foods supplied within a balanced diet.

Another approach to the cholesterol problem has been to block the synthesis of cholesterol within the body. Thus far this approach has been beset by the problem that agents which can successfully block cholesterol synthesis also often block formation of other substances needed for normal body metabolism. In

addition, side effects of some agents limit their usefulness. A liver enzyme, hepatic catalase, has been shown by grantees to successfully limit cholesterol synthesis in animal studies without toxic effects or inhibition of essential precursors of phospholipids and triglycerides. However, more extensive investigation will be needed before it can be considered for clinical trials in humans.

NHI grantees have shown that cholesterol and epinephrine, together or separately, can produce an inflammatory reaction within the walls of large arteries in experimental animals. This reaction is characterized by a marked increase in the extracellular spaces of the vessel wall, probably due to dispersion of elastic and fibrous components, and by adherence of platelets to the inner surface of the vessel. The finding that epinephrine can elicit this reaction may bear on the apparent relationship between stress and heart disease, since stress stimulates the release of epinephrine and norepinephrine from the adrenal glands.

Similar circumstances also may surround the relationship of atherosclerosis to hypertension. It is well known that the development of atherosclerosis in men and animals is accelerated by hypertension. NHI grantees have found in radioactive tracer studies of paired hypertensive and normotensive rats that the rate of cholesterol synthesis is increased in the hypertensive animals.

Coronary heart disease—The concept that physical exercise may confer some degree of protection against the development of heart disease was bolstered in the past year by grantee studies of 8,500 middle-aged members of an Israeli kibbutzim (cooperative settlement) where diet, housing, and other environmental and social conditions are equal. A 10-year study of this group revealed that sedentary male workers had three times as many heart attacks as did manual workers. However, no correlation could be made between serum lipid patterns and the increased incidence of myocardial infarction among the sedentary workers.

Another study of this group by the same investigators showed that, while manual labor appeared to offer protection against heart attacks for a large percentage of the population, those who did suffer myocardial infarctions within the physically active group had the poorest chance of long-term survival. The 5-year mortality rate in this group was 47 percent. By comparison the mortality rate was 32.6 percent among those who did light manual work and 25.7 percent among those in the sedentary group.

Grantees have reported consistently higher hematocrit readings (percentage of blood occupied by the blood cells) in heart attack victims than in age-matched subjects of similar ethnic, social and economic backgrounds. Fifty percent of the heart attack victims studied had hematocrits exceeding those of 90 percent of the control group. These grantees concluded that the relationship between hematocrit and blood viscosity indicates that red cell concentration may significantly influence coronary blood flow. The investigators found that reduction of hematocrit by frequent small bleedings was of clinical value in the relief of angina pain.

The mechanism by which nitroglycerine and other nitrates relieve anginal pain has been the subject of some controversy. Some investigators maintain that these drugs improve the blood supply to the heart by dilating the coronary arteries, others that the drugs merely reduce the workload of the heart to a level more in keeping with its available blood supply. Recent grantee studies have demonstrated that certain of these nitrates, notably glyceryl trinitrate and erthrol tetranitrate, do consistently increase the diameter of the coronary arteries. Unfortunately, these studies did not settle the controversy, since they were unable to determine whether this coronary artery dilation actually increased the blood supply to the heart.

Hypertension.—NIH grantees found that when pregnant rats were subject to high salt or low potassium diets, or were treated with certain hormones or the diuretic drug chlorothiazide, their young developed a form of hypertension closely resembling essential hypertension in man. (The hormones were aldosterone, cortisone, desoxycorticosterone, and progesterone.) The offspring of the treated animals were normotensive at birth, but their blood pressure rose slowly and relentlessly until it reached hypertensive levels by maturity. At autopsy, no severe kidney damage could be seen, but other evidences of hypertension such as enlargement of the left ventricle of the heart and moderate thickening of the arterioles were frequently observed. The investigators concluded that the hypertension was probably produced through some action on the fetal kidney during its early stages of development.

These studies show that prenatal influences can lead to hypertension and possibly other disorders in animals. These findings may also prove clinically important in man.

Surgery.—Open-heart surgical correction of the tetralogy of Fallot, or replacement of mitral or aortic valves with prosthetic devices, often carries with it the risk of wholesale destruction of red blood cells, resulting loss of hemoglobin, and renal shutdown. This damage results, to a great extent, from the prolonged use of the heart-lung machine for the 2 hours or more needed for such operations. NHI grantees found that administration of the drug mannitol reduced red blood cell destruction by at least 50 percent in 19 of 20 patients undergoing this type of surgery, and greatly reduced the risks of such an operation.

Another grantee reported that the same agent prevented acute renal failure, which often accompanies open-heart surgery when prolonged perfusion and deep cooling (hypothermia) is required in the repair of complicated heart lesions. A favorable diuretic response in 1 to 1½ hours was observed in six of eight patients infused with mannitol following surgery. The grantees reported that successful use of the drug depends upon early discovery of impaired urine excretion and quick initiation of therapy before acute renal failure can become irreversible. No cardiorespiratory overloading or other complications were observed with this therapy.

Many complications associated with use of the heart-lung machine to sustain circulation during open-heart surgery have been traced to physiologic changes caused by large quantities of homologous heparinized blood used to prime the machine. NHI grantees have shown, in both experimental and clinical studies, that a 5 percent glucose solution in distilled water can readily substitute for the pooled blood to get the machine started. Studies of two groups of animals showed that kidney function was reduced by approximately two-thirds immediately following bypass in the blood-primed group; whereas kidney function in the glucose-primed group showed little change from control values.

Grantees have also developed a method for pinpointing cardiac shunts and for measuring myocardial bloodflow by using a newly available radioactive isotope, rubidium-84. The decay of this isotope leads to the simultaneous emission of two gamma rays traveling in exactly opposite directions. These gamma rays are detected by means of sodium iodide crystals, placed on opposite sides of the heart and facing one another. They are counted only if both iodide crystals are struck simultaneously. This coincidence counting technique makes it possible to scan very small areas of the heart to measure blood flow and direction or to detect heart defects.

TRAINING GRANTS AND FELLOWSHIPS

The National Heart Institute is supporting over 800 fellowships, training grants, and research career awards. These awards were made through the Heart Institute's program which provides for the training of qualified persons for research and academic careers in basic and clinical sciences related to cardiovascular health and disease.

The Heart Institute awarded \$3,185,000 last year for 431 research fellowships—365 postdoctoral and 66 special. Training grants expenditures amounted to \$11,296,000 for 343 grants, with the largest area of training in medical cardiology. In the research center awards category, \$1,221,000 supported 69 awards, with the largest interest focusing on physiology.

The training program is designed to meet two objectives: (1) to improve the quality of training for cardiovascular research, and (2) to increase and strengthen opportunities for promising young scientists and established investigators for careers in medical research.

Undergraduate training grants help medical schools to provide better teaching of the subject related to cardiovascular disease. Graduate training grants help to establish new training programs in institutions with qualified training personnel, to expand existing training programs, and to establish new programs in areas with critical personnel shortages.

The fellowships program supports research training of qualified scholars for research and academic careers in the basic and clinical sciences related to the cardiovascular area.

Special fellowships support the advanced training of qualified applicants whose needs make other types of fellowship support inapplicable.

The research career award program was created to increase stable full-time career opportunities for scientists of superior potential and capability in the sciences related to cardiovascular areas.

Two types of awards are available—career awards and developmental awards. Career awards help institutions to recruit and keep highly skilled investigators of proved competence and scientific merit. Developmental awards enable institutions to finance positions for qualified scientists who have 3 years or more of relevant postdoctoral research or professional experience.

The training grants and research fellowships programs of NHI are helping substantially to add to the Nation's resources for heart research; and these programs, year by year, demonstrate that they constitute an indispensable component of the Institute's activities and one without which continuing growth and development in the progress of heart research itself could not be attained.

CONCLUSION

As this summary indicates, contributions to new knowledge and improved technology—the substance of heart research—have been considerable during the past year, both in basic fields, such as physiology, and in areas of more immediate application, such as research appraisal of new drugs or development of new surgical techniques.

More detailed descriptions of individual research accomplishments and reviews of progress made in such research areas as epidemiology and cardiovascular surgery are provided by "Highlights of Heart Research" and by the special reports submitted with this statement.

Although progress thus far has been gratifying, much remains to be done. It would be pleasant to be able to say that the battle against cardiovascular disease is all but won—that with a major advance here or a breakthrough there, the war will be over. Unfortunately, the mortality statistics presented early in this statement provide ample evidence that the real fight is only beginning.

In some sectors of the battlefield—congenital heart disease and rheumatic fever, for example—substantial gains have been made. In other sectors, such as atherosclerosis and coronary heart disease, a near stalemate exists. However, in these sectors the buildup of basic knowledge is continuing in the firm conviction that from such knowledge will arise the weapons for future breakthroughs.

In conclusion, Mr. Chairman, the appropriation request for 1964 for the National Heart Institute is \$133,624,000 as compared with the \$117,051,000 available in fiscal year 1963. The request for 1964 will provide for program growth in the following areas:

Research projects.—Additional grants in support of new research in arteriosclerosis, cerebrovascular disease, hypertension, congenital heart disease, rheumatic fever and rheumatic heart disease, heart failure, coagulation defects, cardiopulmonary diseases, and other diseases of the blood and blood vessels.

Fellowships.—Additional postdoctoral and special awards to increase the number of trained heart researchers and to assure the continuing flow of skilled and imaginative workers into the cardiovascular field.

Training.—Additional graduate training grants in the preclinical (basic), clinical, combined preclinical-clinical, developmental, and paramedical research areas.

Collaborative studies.—For establishing a laboratory for research in pathology and comparative pathology to take advantage of the materials available from the diverse population studies already underway.

Review and approval of grants.—Support of increased activities of the Institute staff and National Advisory Heart Council necessary to the expanded grants program.

The request for 1964 is distributed among program activities as follows:

Grants:

Research.....	\$97,183,000
Fellowships.....	6,399,000
Training.....	15,170,000
Subtotal, grants.....	<u>118,761,000</u>

Direct operations :

Research-----	\$10, 608, 000
Collaborative studies-----	1, 426, 000
Training activities-----	250, 000
Review and approval of grants-----	2, 183, 000
Program direction-----	396, 000
Subtotal, direct operations-----	14, 863, 000
Total, 1964 appropriation request-----	133, 624, 000

Dr. KNUTT. I would like to call attention to some of the points that were brought out in the prepared statement, for two reasons.

One is because of the fact that we have had what we consider a real breakthrough in the treatment of hypertension in the past year.

The second reason is to pull together some of the references that had been made to cholesterol in the body of the prepared statement.

First of all, I think it would be important to point out that recently there appeared in the publicity from the American Heart Association a statement that there had been a 6-percent decrease in the death rate from hypertension in this country in individuals between the ages of 45 and 64 years of age.

NEW ANTIHYPERTENSIVE DRUGS

This is probably due to a combination of factors, but one of the most important ones may very well be the development during this period of some new antihypertensive drugs. This brings up the point that in the past year, through a collaborative effort between one of the pharmaceutical houses and the National Heart Institute still another drug by the name alpha-methyl DOPA has been found to be highly effective in reducing blood pressure in about two out of three patients with hypertension.

It is a very powerful agent. The findings so far have been on about 100 patients. They have been treated for periods varying from 2 weeks to several years and after thorough testing the drug has just recently become available on the market. It is known commercially as Aldomet and is produced by Merck Sharp & Dohme. It is derived from one of the amino acids and has powerful action with relatively minor side effects in patients suffering with bad hypertension.

About 10 or 11 years ago, three men, Dr. Stein, Dr. Brown, and Dr. Pfister of Merck Sharp & Dohme, reasoned that norepinephrine and epinephrine which are very potent substances which have to do with the regulation of the blood pressure and which are released at the nerve endings—these men reasoned that the synthesis or the production of norepinephrine or epinephrine might be blocked by inhibiting a step that appears in their synthesis. They thought they could do this by changing a little bit the chemical structure of a substance that was known as DOPA which itself is derived from one of the amino acids which we ingest in protein food. Some of the compounds that were synthesized by these men were found to be capable of modifying the formula of this chemical substance so that it indeed did behave in this way. However, it was felt at the time that this would be interesting only as a research tool in amine metabolism. It was not looked upon for possible use in treating

patients with hypertension but NHI scientists felt it might be useful in patients who had the malignant tumors pheochromocytoma or malignant carcinoid. These tumors are characterized by the secretion of very large amounts of norepinephrine and serotonin, respectively.

So the NIH investigators received some of this material from Merck Sharp & Dohme and there was a series of collaborative toxicity studies in animals after which the drug was given to some of the patients with these malignant tumors. Interestingly enough, they did find that it was nontoxic to humans and they found that it had a very marked effect in reducing blood pressure in humans. Whereas, having been tested in animals, and found to have no effect in reducing the blood pressure in animals, it had this profound effect in humans. This was interesting and important and indicates that perhaps some of our drugs that we find in the future may be potent for use in humans even though they have flunked the animal test.

Mr. FOGARTY. What animal? Several different animals?

Dr. KNUTTI. Several different species of animals to study the effect and toxicity.

Mr. FOGARTY. Would this hold true in the rhesus monkey?

Dr. KNUTTI. I don't think this particular compound was tested in the monkey. I think the usual test animals were rabbits and dogs in this instance. But I would have to check on that. I am not certain about monkeys. I doubt it.

Mr. FOGARTY. All right.

Dr. KNUTTI. This drug has been found to control hypertension in all degrees of severity, in about two-thirds of the cases. It appears to be relatively free of side effects. They had a few untoward reactions, a few cases of mental depression. There was laboratory evidence of some liver malfunction in seven patients but there was no evidence of liver damage and all of these effects disappeared when the drug was discontinued. It has some advantages over some of the other new hypertensive agents. It does not cause certain bowel disturbances that some of them do. It does not affect appreciably sexual impotency in the male as some of them do, and it does not produce some of the very sudden unexpected drops in blood pressure which are sometimes observed in hypertensive patients, especially when they get up in the morning. We feel that this is a very outstanding landmark in the attempt to control hypertension and I wanted to report that to you particularly.

SOURCES AND EFFECTS OF CHOLESTEROL

The other item that I wanted to call attention to, if I may, is to pull some things together about cholesterol, that are referred to in one context or another in the long prepared statement.

I thought with your permission that I would give you a short review of some of the important factors.

Mr. FOGARTY. Go ahead.

Dr. KNUTTI. Cholesterol itself is a powdery, white, tasteless, odorless substance and is found in all animal fats and oils. It is found in egg yolks and in milk. It is the most abundant sterol in animal tissues. It is the only dietary sterol that is absorbed to any extent from the human gastrointestinal tract.

The amount of cholesterol taken in the diet comprises but a small fraction of the cholesterol content of the blood. The great bulk of cholesterol that we have in our serum and in our body tissues is synthesized in the liver. Therefore, diets that are low in cholesterol itself have very little significance in any attempt to lower the blood cholesterol or the total body content of the cholesterol.

The liver itself, as I noted, is the main source of cholesterol. It manufactures cholesterol from a precursor known as acetate and this acetate arises from the earlier metabolism and breakdown of certain carbohydrates and protein substances and also fat. There is a little synthesis of cholesterol that takes place in the adrenal glands and possibly some other tissues make it. I think the brain actually synthesizes small amounts of cholesterol. It is the most important substance in the formation of other sterols in the body. In other words, it is used as a base for the production of certain of the adrenal hormones and other steroid types of hormones.

These sterols include the male and female sex hormones and other hormones associated with the regulation of salt and water metabolism. It also is used in forming the bile acids, the acids found in bile, which play a role in the absorption of fat from the intestinal tract and cholesterol itself is excreted from the body through the bile.

About 70 percent of the cholesterol in the serum is combined with some of the fatty acids to form cholesterol esters and if it were not combined with these fatty acids the cholesterol itself would not be soluble. You would not be able to dissolve it in the body fluids.

This substance accumulates in the inner walls of the blood vessels to form atherosclerotic lesions. It still is controversial how it does it. There may be several mechanisms involved. Two leading theories—one is the filtration theory in which the substance filters through the wall and the other theory is that the blood vessel itself under certain circumstances may manufacture cholesterol.

REDUCING CHOLESTEROL LEVEL IN THE BLOOD

There are a number of ways which have been attempted or thought about to reduce cholesterol levels in the blood. One of the first of these, historically, was limiting the cholesterol in the diet. When we got more information about the volume of manufacture of cholesterol in the liver, it became rapidly apparent that one could not control serum cholesterol concentration by limiting the amount of cholesterol itself that is taken in the diet.

Another very popular theory which I reported to this committee last year was in the use of a substance which interfered with the last step in cholesterol synthesis where desmosterol is formed instead of cholesterol. Cholesterol blood levels were lowered by giving a substance which is known as Triparanol. It was found that cholesterol was replaced by this desmosterol which is chemically very similar to it. Since that initial enthusiasm last year, we have found there are a considerable number of similar precursors of cholesterol. So the importance of desmosterol as such is not materially as great as we thought it was a year ago.

Another way in which we can reduce the amount of cholesterol in the blood stream is by other drugs which act on the synthesis or

by factors that affect its transport from the liver, and it has been found that some of the estrogens, the female sex hormones, play a role in lowering blood cholesterol.

Another way to get at this would be to interfere with the formation of it. Indeed, the accumulation can be interfered with indirectly by metabolizing it quicker than it is formed. The thyroid hormones have been found to be useful in speeding up the metabolism of the substance.

If the cholesterol were excreted faster than it were formed this might be another possible mechanism of lowering it in the blood stream. The other thing that has been found out and which we are engaged in studying in a preliminary way is the effect of certain types of diets with cholesterol levels in the blood. I will defer any further discussion about these projects unless you wish to ask me specifically about them, Mr. Chairman.

In concluding, as a means of realistically viewing the horizons which lie ahead for the research attack on heart disease, the size and nature of the disease problem itself deserve initial attention. That heart disease imposes a vast burden upon health and economy and that it is the Nation's No. 1 killer are strikingly apparent. Last year, deaths from heart disease totaled an estimated 947,210, an increase of nearly 26,000 over the previous year—and far over half of all deaths in the United States.

Gains in research and its application, as well as in implementing new activities that will mean further, future gains, have been made, however, steadily and on wide-ranging fronts. As well as substantial additions to basic knowledge, many advances have been recorded, for example, in heart surgery, in studies of new drugs and their means of action, in improved methods of diagnosis and treatment, and in new instrumentation. Moreover, other research related activities of the National Heart Institute, such as the training grants and fellowships programs, evidenced their values in helping add to the short supplies of trained scientific manpower and make possible continuance of progress in heart research itself.

INCREASES REQUESTED FOR 1964

Finally, Mr. Chairman, the request for the National Heart Institute is \$133,624,000 as compared with the \$117,051,000 available in 1963. The request will provide a net increase of \$16,573,000 for the following items: \$14,522,000 in research grants; \$449,000 in research fellowships; \$1,179,000 in training grants; \$125,000 in direct research for centrally furnished services; \$103,000 in collaborative studies—geographical disease activities; \$50,000 in direct training activities; \$279,000 in review and approval activities, of which \$109,000 is for centrally furnished services. In addition to these increases there is a decrease in program direction of \$134,000 for centrally furnished services.

Mr. FOGARTY. Thank you, doctor.

TEACHING GRANTS TO MEDICAL SCHOOLS

You were here this morning when we talked about these teaching grants to medical schools. Do you contribute \$25,000 to every medical school, or just the 4-year schools?

Dr. KNUTTI. We give \$25,000 to the 4-year medical schools; \$15,000 to the 2-year medical schools and to the schools of public health. We also give \$25,000 to schools of osteopathy.

Mr. FOGARTY. Do you cover all the medical schools?

Dr. KNUTTI. All the medical schools; yes, sir.

Mr. FOGARTY. How do they use it?

Do they match this grant of \$25,000?

Dr. KNUTTI. There is no formal matching arrangement.

Mr. FOGARTY. This is given to the schools for one specific purpose, though; isn't it?

Dr. KNUTTI. That is correct.

Mr. FOGARTY. To teach in this area of heart disease?

Dr. SHANNON. It is more to integrate the teaching of cardiovascular diseases as they occur in the whole variety of departments throughout the entire 4 years in medical school.

Mr. FOGARTY. But it has to be spent for this purpose. It cannot be taken by the medical school to pay for some other costs, can it?

Dr. KNUTTI. That is correct.

Historically, if I may just stay with this one more moment, this program was started in 1948 or 1949. At that time I was on the faculty of a medical school. This was before I came into the Public Health Service. It was really a very remarkable thing what this program did to pull together as one focus in a medical school the total cardiovascular interest. A number of departments were included; basics like pathology and physiology and clinical departments like pediatrics medicine and surgery. There was a program coordinator who headed up the activity and he got all of us who were interested in this field, and formed a real central core of cardiovascular interest in the school. The emphasis then was on improvement of teaching, but it also helped to equip the schools with some instrumentation which served in many schools as their first real cardiopulmonary laboratories. As time has gone on, these units, these central cores which have been supported by the grants have become more and more oriented to the research activities in cardiovascular diseases. I think it has played a large part in interesting medical students in cardiovascular disease, both from the clinical standpoint and from the research standpoint.

Mr. FOGARTY. I was going to add, we have been told that this program is very beneficial from that point of view, that medical students, when they graduate now, have a better grasp of some of the problems of the cardiovascular diseases than they would have had if this grant had not been made?

Dr. KNUTTI. Yes, sir. I would certainly agree with that.

Mr. FOGARTY. I think the people in the Cancer Institute made that point a few years ago, that the people who are coming out of medical schools now know much more about cancer than they would have if this grant had not been made. So your conclusion is that it is a worthwhile practice?

Dr. KNUTTI. It is.

Mr. FOGARTY. Do you think it ought to be increased or do you think \$25,000 per school is enough?

Dr. KNUTTI. I think that \$25,000 is helpful.

Mr. FOGARTY. Heart disease still kills more people in this country than all other diseases put together, does it not?

Dr. KNUTTI. Yes, sir.

CORONARY THROMBOSIS

Mr. FOGARTY. What about your work in coronary thrombosis problems?

Dr. KNUTTI. We have a wide range of activities in the coronary thrombosis problem. I suspect that you may be referring to the diet studies and cholesterol?

Mr. FOGARTY. I was going to ask that as a separate question—about diet. We mentioned it in our report last year. Is there anything else that you could report as progress in this area?

Dr. KNUTTI. I think that we have taken the first step in something that may prove to be very exciting. There have been developed over the past few years, and have been known for years longer than this, certain agents that interfere—certain agents that dissolve blood clots. These are known as thrombolytic agents.

Mr. FOGARTY. Do you know what causes coronary thrombosis yet?

Dr. KNUTTI. Well, we know the mechanism, the pathology of what takes place when a coronary artery thrombosis occurs, but we do not know the specific etiology or causative agent if, indeed, there is just one agent.

Mr. FOGARTY. It happens to people in the prime of life, too; does it not? The coronary seems to hit people in their 40's quite often.

Dr. KNUTTI. Very frequently; sometimes earlier than that.

Mr. FOGARTY. Take the average coronary. What would you tell a patient who has had one to do? If he takes care of himself the average person can expect to live a long time, can't he?

Dr. KNUTTI. There are many instances on record, Mr. Fogarty, where people have lived the normal lifespan after having had a coronary.

I think the best advice that one could give to such a patient would be to lead a reasonably moderate life, eating the proper things, not getting obese, probably not smoking, getting an adequate amount of exercise.

Mr. FOGARTY. How many years can the average person expect to live if he does this?

Dr. KNUTTI. I would have to look up the statistics on this. I cannot quote them.

I could furnish them to you.

(The information follows:)

CORONARY SURVIVAL STATISTICS

Recent data on prognosis following first attacks of myocardial infarction including all cases from the population at large, whether or not they reached a hospital, indicate that the immediate mortality from the first attack may be as high as 34 percent. However, for those who survive the immediate period of the first attack, approximately 80 percent will be alive after 5 years and more than half will be alive 10 years following the first attack.

Dr. SHANNON. Mr. Fogarty, can I make a comment? We have increased information that we have a substantial number of people who had an infraction during the mid forties. There is no average patient. It depends on his age, the size of the infarct; it depends on the state of the remainder of his vessels.

I would say people in their 40's have a guarded but very good prognosis for a substantial, quite long life.

Mr. LESINSKI. The mental attitude is your basic problem.

Mr. FOGARTY. Not nutrition?

Mr. LESINSKI. Mental outlook is the basis of the whole thing.

INCREASE REQUESTED FOR 1964

Mr. FOGARTY. Doctor Knutti, the appropriation for 1963 adjusted for comparability is \$129,793,000 and the request for 1964 is \$134,059,000, an increase of \$4,266,000. However, in the adjustments is a reserve of \$12,177,000, so the actual spending rate proposed for 1964 is about \$16½ million more than 1963. Is that right?

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. How much of that reserve of \$12,177,000 is forced savings?

Mr. KELLY. \$1,177,000.

Mr. FOGARTY. What accounts for the balance?

Mr. KELLY. The \$11 million is in a reserve for contingencies and it is on the basis that the prediction of the number of approved projects at the time the apportionments were made indicated that these funds may not be required but it was understood that if circumstances were to result in receipt of approvable projects it would be reconsidered.

GERONTOLOGICAL RESEARCH BUILDING

Mr. FOGARTY. You are asking that language be included in the bill extending the availability of funds for planning the gerontological research building until June 30, 1964?

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. Why is it taking so long to plan this building?

Dr. KNUTTI. The appropriation was from fiscal year 1962 funds. This has been a rather unique experience in that there have been a number of unforeseen problems in developing plans sufficient to have release of the funds for the purpose.

One of the problems, and not one of the least problems, was the actual negotiations between the municipal government and the Federal Government in arranging for the transfer of land, the deed of land on the ground of the Baltimore City Hospital to the Federal Government in order to put up a Federal structure.

This took some time, had to go through the Baltimore City Council, their board of estimates, the mayor, and there was quite a bit of preparation and time-consuming negotiation involved in this particular aspect.

It was also unique in the experience of many of the people who reviewed the program because this was a building which provides for research being carried on, not under the direction of the Federal Government, but as a collaborative research on the part of local institutions. In the passage of the proposal through channels there were questions raised which had legal connotations and these had to be discussed with legal counsel before they were cleared.

Mr. FOGARTY. Are you in pretty good shape now?

Dr. KNUTTI. The money has been released and we are now in the process of selecting an architect.

The deed has been made and we are going to move forward as quickly as we can, but we are not going to be able to finish the planning during this fiscal year. That is why we have the request for continuation of the planning funds.

SPECIAL REPORT

Mr. FOGARTY. We will place your special report regarding this facility in the record.

(The report follows:)

THE GERONTOLOGY BUILDING

With funds provided by the Congress for the purpose, activities are progressing for the planning of a new physical facility for the functional research program in aging of the National Heart Institute. The building is to be constructed on the grounds of the Baltimore City Hospitals, Baltimore, Md., on a site given to the United States by the city of Baltimore.

The physical scope of the facility program includes the construction of a medical research building, with supporting features for the basic building such as built-in and installed types of equipment, complete utilities systems, and all-weather passageway connections to existing hospital buildings closely involved in the research that will be conducted in the new building.

The new building will also provide for a number of central services indispensable to the conduct of research and necessary for the general use of collaborating programs. These services will include animal resources, shop facilities, photographic and art services, computing services, and general administrative services.

PROGRESS IN PLANNING AND CURRENT STATUS

During the past year, progress has been made in planning for the new gerontology building, including discussions and meetings on various aspects both of the physical facilities themselves and of the research programs that will be provided for in the building. With the recent release of planning funds, further definite progress is being made toward delineating and defining, in terms of the needs and available resources, the actualities of the new construction, the operating and financing responsibilities, and other factors; and mutual agreements have been arrived at by the Federal Government and the city of Baltimore.

Thus, planning is now moving ahead at an accelerated pace, with frequent meetings, negotiations, and planning sessions to the present time and further work scheduled in coming weeks.

The NHI appropriation for fiscal years 1962 provided \$1 million for planning for the building. The planning funds have recently been made available to the NHI. Our planning is based on a total estimated cost of \$7.5 million for the building, exclusive of planning funds. The next step is the selection of the architect and the preparation of plans and blueprints. The process of selecting an architect has begun and it is hoped that the selection will be made and that the architect will begin his work soon.

When completed, the new gerontology building will provide increased opportunity for productive new research on the complex problems of aging. One of the major needs in this field today is for multidisciplinary research ranging from basic studies at subcellular levels to investigations of aging in individuals and groups. These kinds of research will be carried on, utilizing the new facility, by closely related groups: the Gerontology Branch of the National Heart Institute, the collaborative research programs of the Baltimore City Hospitals, and collaborative research groups of the Johns Hopkins University, University of Maryland, and other regional, State, or national institutions and agencies concerned in the aging problem.

GERONTOLOGY BRANCH, NHI

The activities of the Gerontology Branch emphasize investigations of the basic biological mechanisms of aging and the description and interpretation of age changes in the various organ systems of the human, as well as overall changes in performance and behavior. The depth and range of these scientific

investigations is indicated by the scientific disciplines represented in the activities of the Gerontology Branch, such as—

- Cardiovascular-renal physiology.
- Metabolism and endocrinology.
- Pulmonary physiology.
- Human performance.
- Experimental psychology.
- Physiological psychology.
- Comparative and cellular physiology.
- Morphology.
- Nutritional biochemistry.
- Comparative biochemistry.
- Biophysics.
- Molecular biology.

The expanded basic studies of the Branch's scientists will involve a variety of animal species ranging from single-cell protozoans through insects, rats, mice, subhuman primates and, of course, man. The new facility will make possible, through its resources and space, investigations not now possible of many aspects of genetic and environmental conditions of a variety of species, including colonies which have been reared to advanced ages.

In addition to basic studies on the mechanisms of aging, it is also important to find out more about the effects of age in human subjects. The new facility will provide new research opportunities in this regard and the Branch will be able to undertake new kinds of studies of human subjects precluded by present limitations of available facilities.

New studies of various disease processes affecting older people will also be conducted, including a wide variety and range of types of patients of the Baltimore city hospitals. Moreover, further studies will be carried out through the hospitals' connections with families, nursing homes, boarding homes, and a planned 300-unit public housing project to be constructed on the city hospitals' grounds. These affiliations will permit research into the social problems of the aged and involve studies on normal subjects as well as those suffering from various disease states.

COLLABORATIVE RESEARCH: VARIOUS AGENCIES

In order to provide a comprehensive research center for aging in the new Gerontology Building, it is planned to carry on collaborative activities with local, regional, State and National agencies and institutions.

The new facility will provide opportunity for needed epidemiological studies in the field of aging. Solution of many problems of the aging requires a detailed knowledge of a wide variety of social, economic, and cultural characteristics of individuals living in the community.

The incidence of disease and disability in specific communities must be determined according to age. Many types of communities (rural, suburban, metropolitan) are available for study in the region. These programs can be developed by the PHS in collaboration with such organizations as the Maryland State Commission on Aging, the Maryland State Health Department and the Johns Hopkins University School of Hygiene and Public Health.

Another facet of the new Gerontology Building, which will enhance its value as a regional center and comprehensive aging research resource, is its provision of laboratory facilities and resources such as colonies for rearing animals to advanced ages. Here visiting scientists and investigators from other institutions can carry out significant studies of aging animals. Such facilities and colonies are, practically, nonexistent today and the provision of this new resource can be expected to attract scientists of the highest caliber. Their presence and work in the new Gerontology Building will contribute stimulation and encouragement to other research there, the personal interchange of significant knowledge, and important research findings themselves.

One of the major factors limiting research on aging is the difficulty in obtaining animals of known advanced ages, as mentioned above. The rearing of animals to senility poses special problems which can be met in few animal colonies maintained by medical schools and universities. Furthermore, it is not possible to ship aged animals without excessive losses due to death of the animals. In order to resolve this dilemma, the Gerontology Building will provide laboratory space and facilities which will make it possible for investigators from other

universities to come here to use aged animals which have been reared in the animal colony.

COLLABORATIVE RESEARCH : BALTIMORE CITY HOSPITALS

The proposed research building will contain portions of the collaborative research programs to be conducted by the staff of the Baltimore City Hospitals, many of whom are on the faculty of Johns Hopkins or the University of Maryland. These programs, directed toward the basic problems of the function of organs and cells in terms of how they control their environment, and how they are influenced by alterations in their environment, will be conducted by members of the Divisions of Pathology, Medicine, Psychiatry, Surgery, Pediatrics, and Anesthesiology.

Working in the same environment with the NHI Gerontology Branch, these groups of the Baltimore City Hospitals represent the third major aspect of the overall, comprehensive activity in aging. The Baltimore City Hospitals' resources themselves constitute a unique contribution to the whole, since they consist of (1) a group of basic and clinical scientists who are already engaged research on various aspects of aging, (2) a teaching hospital with a full time staff oriented toward and actively engaged in research, (3) a wide range of patients available for study in various divisions of the hospital, (4) a public housing project which will make available additional subject material, and (6) an active teaching program conducted by the staff of the Baltimore city hospitals.

The research of the hospitals' divisions mentioned above will range a wide front, from pathological studies of organs and tissues to studies of techniques for the replacement of diseased organs and tissues by transplantation, and will be conducted in close collaboration with, and continuing interchange of information between, scientists of the Gerontology Branch and others, such as eminent visiting scientists, engaged in the expanded research attack on aging made possible by the new building.

CONNECTION OF DIET WITH HEART DISEASE

Mr. FOGARTY. Last year in our report we encouraged you to give more attention to the connection of diet with heart disease.

What are you doing to carry out the committee's wishes?

Dr. KNUTT. About 2 years ago a planning committee was set up under the chairmanship of Dr. Irvine Page to plan a study which might possibly point out the effect on atherosclerosis of reducing cholesterol levels in the blood in human subjects by means of changes in the diet.

Finally, after setting up the committee and rather intensive study, a series of applications, based on a common protocol which each of the investigators would use in order to make these studies statistically valid, were submitted to the National Advisory Heart Council. At a meeting of the Council last fiscal year the Council recommended approval of six studies. These have to do with the feasibility as to whether or not it is practical or possible to do a larger significant study on the basis of the protocol which has been evolved by the planning committee.

The pertinent points in testing the feasibility have to do with, No. 1, can the average free-living, presumably healthy working male between the ages of 45 and 55 stay for a long time on a diet that has been modified?

In other words, what will be the dropout rate? If the dropout rate is high enough, then it would not be feasible to do the study because in order to make it statistically significant many thousands of people would have to be tested who had stayed on this diet over a significant period of time.

That is one of the important points in testing the feasibility. Another important point is whether or not this can be done by the double blind technique.

Mr. FOGARTY. There is a big difference between the work a person does, too. Sitting down like I am, all day, or out shoveling, digging ditches, laying brick or something like that all day.

Mr. LESINSKI. That is when you felt good.

Dr. SHANNON. To take care of that aspect you match the test versus the control diet. The primary problem in all this is to have some test point in the determination of the effectiveness of diet and this would mean—the best indication would be an acute myocardial infarct, thrombosis or the like.

This occurs in a given restricted age group or in a given population group which has sufficiently low attack rate that the size of the group has to be large to compare the results.

We know that psychological factors such as knowledge of what one is doing, problems of motivation and all the other things will affect not only whether one will stay on the diet or slip off it, but in addition to that it will have some effect on the net biological effect of the procedure.

The emotional attitude of the patient over a long period of time beyond any doubt has a fairly profound effect on the underlying biology.

This is the reason for the double blind part of the experiment—when the patient does not know whether he is on a low saturated diet or one that has the normal amount of saturated fats.

There is some question that however important this knowledge may be the question is whether or not in a diet study of this general sort it is reasonable to expect this type of information to be withheld from the patient or if there can be a sufficient control as to make the experiment definitive.

The importance of this is not only the cost but it will involve a very large number of people in an investigation over a substantial number of years and unless it has been definitely demonstrated that this will result in definitive information it is not worth while.

Mr. FOGARTY. Is Dr. Stare, from the Harvard School of Public Health, involved in this?

Dr. KNUITL. He is one of the six who are conducting the study.

STUDY OF FRAMINGHAM, MASS., GROUP

Mr. FOGARTY. Do you have any progress to report from your study of the people in the city of Framingham, Mass.?

Dr. KNUITL. This project is going along very satisfactorily. It was started out on the basis of a 20-year study of a group of I think, some five or six thousand people.

The study has now reached the stage where some of the people who initially went into it are dying and in the past year or two we have had to shore up the pathology facet of the program which it had not been necessary to do before, to allow for an increased number of post mortem examinations.

So it has gone into that phase and in the meantime they are continuing the periodic examinations of the living subjects.

Some of the other institutes have been interested in using this highly selective population for some work of their own.

I think that the Arthritis Institute has been supporting some work relative to the rheumatoid factors that are present in this population.

It has been a very productive program in terms of publications, and scientific observations, that have come out of it. It has really, I believe, stimulated and led the way to new ideas in the epidemiology of coronary heart disease and atherosclerosis.

COLLABORATIVE GEOGRAPHIC RESEARCH

Mr. FOGARTY. A year ago we also encouraged you in your geographic studies.

Do you have anything to report on that?

Dr. KNUITL. Yes, sir. We got underway, the 1st of January, I believe, after considerable negotiation, an epidemiologic study in Israel which is headed by Dr. Groen.

Mr. FOGARTY. Just this past January.

Dr. KNUITL. Yes, sir.

Mr. FOGARTY. What is his name?

Dr. KNUITL. Dr. J. J. Groen.

We have assigned one of our epidemiologic officers to help out with the projects over there. This is a study that is based on some of the things that have been found out at Framingham, only in this instance various ethnic populations are being used.

Israel is one ideal place to do a study like this because they have this in that country, several ethnic groups. They also have new citizens coming in all of the time.

So we can study what has happened in the people who have lived there for some period of time, and also study the status of people who have lived other places in the world like in Yemen for example, when they first come to Israel and follow them to see what changes if any they may develop later on which would be comparable or uncomparable to the Yemenites who have lived in Israel over the years.

So this study is going forward. There is another study that we are getting ready to start in Puerto Ricans who have, in their native habitat, at least, quite a low incidence of coronary heart disease.

It is important to see if we can evaluate the reasons for this and then compare these with some of the Puerto Rican population in this country who have lived here for a number of years and have become completely acclimated as far as their diet and living circumstances are concerned.

Another study that we are contemplating is taking advantage of the unique population that is in Hiroshima in Japan. The AEC has been studying it from other standpoints as well as from the cardiovascular status.

The Japanese are noted to have an extremely low incidence of coronary thrombosis but a very high incidence of cerebrovascular atherosclerosis.

To compare these native Japanese with the domestic Japanese and, as Dr. Endicott mentioned yesterday, those in the intermediary stage in Honolulu, may bring out some features about these conditions that we do not now know about.

Mr. FOGARTY. Is not that also so in China?

Dr. KNUTTI. I am told that it is the same in China.

Mr. FOGARTY. A few years ago we were told it was low there and some people told the committee that they thought it was because of the rice diet, and low calorie intake.

Dr. KNUTTI. We have had correspondence with a professor of public health in the National University in Taipei. He was interested in studying the situation there and he tells essentially the same story that we hear from the Japanese.

In Formosa they are said to have a very low incidence of coronary thrombosis.

COMMUNICATION WITH PROFESSIONAL PEOPLE IN COMMUNIST COUNTRIES

Mr. FOGARTY. What is your line of communication with some of these countries behind the Iron Curtain? Are you able to communicate with them on a professional basis?

Dr. KNUTTI. We have no relationships at all with Red China—none whatsoever. But we do have an exchange agreement with the Soviet Union and we have had occasional missions of the Soviet representatives coming here. As a matter of fact, Dr. Miasnikov, from Moscow, was here last fall with his group and Dr. Watt who was my predecessor in the Heart Institute was over there a couple of years ago. These exchanges are continuing.

Mr. FOGARTY. I remember that. But no communications with Red China at all.

Dr. KNUTTI. No, sir.

Mr. FOGARTY. Even on a professional basis.

Dr. KNUTTI. No, sir.

Mr. FOGARTY. Have you made any attempt to?

Dr. KNUTTI. No, sir.

Mr. FOGARTY. You have not?

Dr. KNUTTI. No, sir.

Mr. FOGARTY. Why not?

(Discussion off the record.)

Dr. TERRY. We have had fairly good contacts with the Russians and most of those satellite countries.

As Dr. Knutti referred to this exchange which was set up in the field of heart disease, it was one of the earliest of the three categories—cancer, poliomyelitis, and heart—agreed on in the field of health.

It was in 1960 when the first Russian mission came to this country. Later a group of cardiovascular scientists met with them in Rome in September of 1960. Then a group from the Heart Institute in the cardiovascular field in this country went to Russia last year and then they have had a group visit here.

In addition, we visited in Rumania and Bulgaria. Dr. Paul White, Dr. Ancel Keys, and Dr. Michael DeBakey and I were in that group.

We had some fairly close working relationships with them and with the Poles and we have a fair degree of information of what is going on in Czechoslovakia, Yugoslavia, but practically nothing from Albania or Hungary.

But we have—I think we are pretty well informed of what is going on in the cardiovascular field in most of those countries.

Dr. KNUTTI. To amplify just one point Dr. Terry mentioned, I neglected to mention a program that is already getting underway in Yugoslavia in our geographic program. Also, we are considering the possibility of starting one in Poland.

Mr. FOGARTY. You are doing something in Italy, too, are you not?

Dr. KNUTTI. Not directly. Some grants, yes. But no collaborative geographic research.

Mr. FOGARTY. I remember Dr. White saying several years ago that he and I believe Ancel Keys went to Italy and stayed there a couple of months. He talked about the Naples area where food was short and people were not getting enough to eat, and he could find hardly any coronary cases in the hospitals. But when he went up around Bologna where there were dairy products and food was more plentiful there were 15 times as many coronaries.

Is that about right?

Dr. KNUTTI. That is a fair statement. It is observations such as these, too, which have led to the impetus behind the necessity for really finding out where a feasibility study of the type I described can be done.

Dr. TERRY. Dr. Keys, Ancel Keys, was the one who headed up some of those studies.

He has had other collaborative studies with groups in Finland, in the Greek Islands, and in Japan—not all, but some of his support of these studies came from the Heart Institute.

They had some very intensive studies in population groups.

LEVELING OFF OF RESEARCH GRANTS PROGRAM

Mr. FOGARTY. Most of the increase you are requesting is \$14,522,000 for the research grant program, but I notice your budget is like the budgets for most appropriations in the Public Health Service. That is just a leveling off. You plan to finance exactly the same number of new projects in 1964 as in 1963; is that right?

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. Do you have any idea as to whether or not you will have more applications for new projects in 1964 than you had in 1963, approvable projects?

Dr. KNUTTI. This varies from year to year, Mr. Fogarty, but according to our estimates—

Mr. FOGARTY. Generally going up though, isn't it? Over the years? Has not your experience been that it is generally on the upward side?

Dr. KNUTTI. In fact, it has varied considerably.

We had some figures on that, I believe.

Mr. FOGARTY. Put them in the record.

Dr. KNUTTI. Yes, sir.

(The information follows:)

New research grant projects, 1958-63

Fiscal year	Number requested	Number approved
1963 (estimated)	1,022	568
1962	915	460
1961	854	458
1960	905	561
1959	642	418
1958	535	329

Mr. FOGARTY. You have not made so much progress in this problem of cardiovascular disease that you feel you can just start taking it easy now and level off or go downhill?

Dr. KNUTT. Indeed we have not. As a matter of fact, the more we are in it, the more really that we know—that we have just scratched the surface to date in implementing programs and planning programs. There is always a lag period before things get started.

CATEGORICAL CLINICAL RESEARCH CENTERS

Mr. FOGARTY. Why are you cutting back the categorical clinical research centers from \$3 million in 1963 to one million six hundred in 1964?

Dr. KNUTT. This, Mr. Chairman, is a sum of money that is used for resources, for the resource portions of the categorical clinical centers.

We have at the present time 28 such centers and of those there are only 13 who requested any resource money.

This center money as it is earmarked in the budget is for the exclusive resource portion, in other words such things as hospital beds, renovation.

Mr. FOGARTY. I understand that, but I am wondering why you are cutting back.

I thought this was a real good idea when it was suggested 2 or 3 years ago not only in heart but cancer, and other categorical areas. I thought you had plenty of places where this sort of program could be set up.

Are you running into difficulty?

Dr. KNUTT. This reflects to some extent the situation within the medical schools themselves. Now, cardiovascular disease as it is taught from the clinical standpoint in the medical school is chiefly the concern of three departments, department of medicine, which embraces the bulk of clinical cardiovascular disease.

This is in the adult patient. The department of pediatrics has to do with congenital heart disease and other heart diseases of childhood like rheumatic fever. The department of surgery of course is responsible for the surgical treatment of heart disease.

In the department of medicine there are many other clinical interests, and cardiology is but one of several such interests. Gastroenterology, hematology, infectious diseases, and metabolic diseases are others.

So that some of the institutions of medicine have felt that they would have sufficient numbers of beds for clinical study on cardiovascular patients from those awarded through the program that is administered by the Institute of General Medical Sciences. This is the noncategorical multidisciplinary type of research bed unit and in most of these units there is cardiovascular research going on.

So in only 13 of the 28 centers have we supplied funds for this resource portion. This I am sure was not foreseen when the program was started. And I would suspect that there would not be much growth in this particular type of support beyond what we have except for the extension to some schools who do not have it now.

Mr. FOGARTY. Do you have any statement in the justifications showing what progress you have made in this program since it has been in effect and where you have established these centers?

Dr. KNUTT. I can furnish that to you.

Mr. FOGARTY. Furnish that for the record.

(The information follows:)

Categorical Clinical Research Center funds are used by the National Heart Institute to support discrete clinical units consisting of contiguous beds and ancillary facilities for studying patients in broadly based cardiovascular research programs. These programs are a type of project which usually involves long-term research activity directed toward a range of problems within the area of cardiovascular disease.

Currently, there is a limited demand for these clinical resources supported by the funds earmarked for categorical centers. This situation can be attributed to: (1) The increasing availability of research beds for cardiovascular clinical investigations with the rapid expansion of the General Clinical Research Center program has minimized the need for separate categorical clinical research facilities, and (2) most investigators prefer to have the flexibility inherent in the use of "nondiscrete" beds, for which these funds cannot be used, so they can study pediatric, geriatric, psychiatric cases in clinical settings more appropriate than a discrete cardiovascular unit.

Following are examples of research programs which are supported in part from clinical research center funds:

1. "Studies of the relationship of emotional stress to cardiovascular disorders, particularly coronary artery disease and essential hypertension." The effect of emotional stress on the development of heart disease is a controversial question, and one which this study is attempting to answer. Under this grant, experimental studies are being carried out on research patients who are given a "stress interview" and measured for changes in the circulatory system before, during, and after such interviews.

2. "Interdisciplinary studies on atherosclerosis, with particular attention to the role of lipids." A difficult problem is undertaken in this study in determining the blood flow through internal organs. It is being studied in research patients with the use of radioactive materials to measure blood flow through the kidney and the blood vessels of the brain and the heart.

3. In another study, pumps which are placed outside the body are used to replace the function of the heart during surgery and assist the circulation in heart failure. In addition, the type of congenital heart defects which damage the lungs by increased blood flow and pressure are produced in dogs to study the manner in which the pressure affects the pulmonary blood vessels. Finally, children with heart defects are intensively studied before and after operations. Growth and development are also studied in regard to heart function and neurologic and psychological functions are evaluated.

4. "Studies of cardiovascular diseases, with particular emphasis on improving cardiovascular surgery." Improvement of techniques for determining whether valves within the heart are functioning adequately is being undertaken in collaboration with engineers who are developing more refined methods for measuring valvular adequacy. The replacement of diseased valves by prosthetic devices is another aspect of this research which is being helped by a special plastics laboratory working on the development of valves which stimulate normal functioning.

In our judgment, the clinical resource portion of the National Heart Institute program will experience no significant growth in 1963 and it is probable that future requirements will not exceed our present total commitment of \$1,310,377, and will continue to decline in subsequent years. This trend, however, should not be interpreted as an indication of what we can expect from these projects in total, since there continues to be an increased demand for support of the basic research activities associated with the clinical research units.

*NHI projects having received support from clinical research center funds,
fiscal year 1961-63*

	Fiscal year 1961		Fiscal year 1962		Fiscal year 1963	
	Total award	Clinical resource portion	Total award	Clinical resource portion	Total award	Clinical resource portion
1.....			\$196, 128	\$148, 669	\$237, 656	0
2.....			191, 664	117, 725	75, 841	\$32, 875
3.....			456, 484	218, 883	233, 900	192, 100
4.....	\$263, 224	\$136, 624	285, 775	102, 801	367, 819	104, 366
5.....			111, 108	101, 105	108, 144	39, 063
6.....	274, 549	216, 661			227, 657	28, 340
7.....	315, 975	315, 975			245, 784	103, 485
8.....			230, 000	192, 628	241, 500	114, 934
9.....			65, 614	38, 503	105, 097	52, 850
10.....					321, 769	66, 460
11.....			261, 813	191, 206	186, 616	99, 684
12.....			81, 350	45, 650	84, 153	84, 153
13.....	129, 500	119, 619	683, 850	144, 000	547, 042	176, 328
14.....	462, 042	309, 092	506, 855	0	648, 359	0
15.....	498, 835	195, 324	870, 201	0	846, 833	0
16.....	199, 547	166, 284	360, 116	0	420, 394	0
17.....	41, 133	15, 523	61, 171	0	65, 371	0
18.....	78, 134	21, 257	75, 884	0	437, 951	0
19.....	453, 706	335, 143			375, 000	0
20.....	466, 651	293, 551	649, 385	0	683, 000	0
21.....	377, 600	228, 100	468, 450	0	468, 450	0
22.....	800, 000	622, 800	781, 106	0	800, 000	0
23.....	653, 709	653, 709	122, 733	122, 733	215, 739	215, 739
24.....	67, 067	47, 267	61, 587	0	68, 462	0
25.....	177, 866	146, 126	474, 871	0	487, 500	0
26.....	159, 070	138, 945	139, 360	0	175, 000	0
27.....			220, 059	220, 059	238, 651	0
28.....			190, 403	138, 038	210, 316	0
Total.....	5, 418, 608	3, 962, 000	7, 545, 967	1, 782, 000	9, 124, 004	1, 310, 377

NHI projects currently receiving support from clinical research center funds

[Fiscal year 1963]

	Total award	Clinical resource portion	Location
1.....	\$75, 841	\$32, 875	St. Louis University, St. Louis, Mo.
2.....	233, 900	192, 100	Temple University, Philadelphia, Pa.
3.....	367, 819	104, 366	Harvard University, Boston, Mass.
4.....	108, 144	39, 063	Meharry Medical College, Nashville, Tenn.
5.....	227, 657	28, 340	University of North Carolina, Chapel Hill, N.C.
6.....	245, 784	103, 485	University of Alabama, Birmingham, Ala.
7.....	241, 500	114, 934	Hahnemann Medical College, Philadelphia, Pa.
8.....	105, 097	52, 850	Northwestern University, Chicago, Ill.
9.....	321, 769	66, 460	Michael Reese Hospital & Medical Center, Chicago, Ill.
10.....	186, 616	99, 684	Seton Hall College, Jersey City, N.J.
11.....	84, 153	84, 153	Oklahoma Medical Research Institute, Oklahoma City, Okla.
12.....	547, 042	176, 328	Baylor University, Houston, Tex.
13.....	215, 739	215, 739	University of Pennsylvania, Philadelphia, Pa.
Total.....	2, 961, 061	1, 310, 377	

COST OF OPEN HEART SURGERY

Mr. FOGARTY. Why is it so expensive to perform open heart operations and these operations on children because of congenital defects?

I asked the question of Dr. Lillehei and the average was around \$2,500 or something like that. Many parents just cannot afford that. This does not seem right to me at all. I know you have no control over the cost.

Dr. SHANNON. The first thing to appreciate—this is a very costly procedure and involves a substantial period of hospitalization but not simple hospitalization.

In order to diagnose, in a highly qualitative way, how large the defect is, requires 7 to 14 days of very intensive physiological study.

The operational procedure itself, particularly on open heart surgery, involves a very large group of people, not on a standby, but very actively participating.

Mr. FOGARTY. I have seen one of them.

Dr. SHANNON. For the period of 2 or 3 days thereafter there is around-the-clock nursing, and there is a substantial period of recovery. So the cost of the operation, that is the unit costs with the associated procedures, is very high.

I think it was the hope initially that when the Children's Bureau could make grants available to the States it would be possible with these funds together with what the community could contribute to make this operative procedure more generally available.

Mr. FOGARTY. We have not listened to the Children's Bureau yet, but in my State it has not worked out.

Dr. SHANNON. There is little chance of reducing the cost at this point in time.

There is a second problem equally important. We spoke of Dr. Lillehei. While most of this procedure can be done in most modern hospitals, there are still many of the open heart type that can only be done in a very limited number of hospitals. As a matter of fact, most of the cardiovascular surgery of any complex nature is done in Minneapolis. It is a setup particularly for that purpose.

It seems unlikely that these skills will be spread sufficiently so that you will have many specialized units because the associated diagnostic equipment is so complex.

Mr. FOGARTY. Mr. Denton.

EXPANSION OF TRAINING PROGRAMS

Mr. DENTON. Aside from the research grants, the only significant increase you have is \$1,179,000 for training.

What part of the program are you expanding?

Dr. KNUTH. We are planning, Mr. Denton, to put more emphasis on the training for clinical investigation.

In other words, to turn out physicians who are skilled not only in the clinical aspects of medicine, but who have specific training in some basic sciences that correlate with research on patients.

There is a need for this type of clinical investigator over the country. With the advent of the new clinical investigative facilities we feel that there will be an opportunity for our medical schools to train very highly specialized investigators in these areas.

Mr. DENTON. What is the program in connection with developmental research areas?

Dr. KNUTTI. If I understand your question correctly, sir, you mean the relation of the training program to the research area?

Mr. DENTON. Yes.

Dr. KNUTTI. The training programs of the Heart Institute are all oriented toward training individuals for research or for academic positions in which research is necessary.

In other words, we are not engaged in training cardiologists or practicing surgeons or practicing paramedical personnel of the type of training that Dr. Felix told you about earlier but simply in training for research.

Mr. DENTON. I wish you would look at page 233 in the justifications. You mention "Developmental research areas" and "Paramedical research." That has to do with the training program?

Dr. KNUTTI. Yes, sir.

Mr. DENTON. Would you address yourself to those two and explain just how they fit in with the training program.

Dr. KNUTTI. These two items are not embraced in what I just finished talking about.

I spoke about the other, the first three items on the previous page, preclinical basic research, clinical research and combined preclinical and clinical research.

DEVELOPMENTAL RESEARCH TRAINING

Mr. DENTON. Tell us about the developmental research.

Dr. KNUTTI. The developmental research program is one which was started about 3 years ago with the hope at the time it was started that in some of our community hospitals there was enough research interest and enough research know-how in some of these areas to make it possible to train individuals in these specific communities who could participate in research programs.

This had partly to do with training house officers in research, and partly with training practicing physicians so they could participate in a research program.

This at the time it was started was viewed as a potential resource where certain types of studies might be carried out, such as drug testing on a very closely controlled basis or other types of studies which would lend themselves to collaborative efforts.

Mr. DENTON. How many would you have in that program?

Dr. KNUTTI. We have 31 participating institutions. The decision has recently been made not to increase this program and, in fact, it was started out I have been told, because I was not here when it was started, with the idea of an experimental approach as to the feasibility of expanding such a program.

Mr. DENTON. Look at the justifications, Doctor? It looks to me like you are increasing the number of institutions from 31 to 37 and the trainees from 131 to 155.

Dr. KNUTTI. I am sorry, I missed that point. It is being expanded on a very small basis, but we do not want to expand significantly until we have a thorough evaluation of the results of the program and are satisfied that this is feasible. We are presently engaged in such a

study. It may prove that additional units are not needed, or to the contrary.

Mr. DENTON. These are the research centers that we set up 2 or 3 years ago at different universities?

Dr. KNUTTI. No, sir. They are in community hospitals in the country.

Mr. DENTON. I see.

Dr. KNUTTI. They are not connected with universities.

PARAMEDICAL RESEARCH TRAINING

Mr. DENTON. What about the paramedical research? Tell me about that.

Dr. KNUTTI. This is a small number of grants that are used specifically for training people who are engaged in research activities that are carried on by professional people.

For example, in research, in the surgery of cardiovascular disease, it is necessary to have very highly specialized trained nursing personnel, also technicians to operate the very intricate heart lung machines and social service workers to assist in a very careful followup of patients after they have been discharged from the hospital.

This again is a small program that has been proceeding on an experimental basis and after study and evaluation we will make the determination as to whether or not to recommend further expansion of it.

TREATMENT OF STROKES

Mr. DENTON. Is there anything new about treating strokes?

Dr. KNUTTI. Quite a bit has been developed in treating strokes in the past few years insofar as that type of cerebral vascular accident is concerned that happens as a result of thrombosis of one of the major arteries leading to the brain.

Mr. DENTON. You can operate on those?

Dr. KNUTTI. Yes, sir.

Mr. DENTON. I have a friend who was operated on for one.

Dr. KNUTTI. Yes, sir.

Dr. SHANNON. The greatest change here is the ability to cope with the disease after it happens—the rehabilitative techniques, so these people can then be returned to active life at a very early stage instead of being incapacitated for the remainder of their life.

Mr. LESINSKI. Is that a blood clot in the vein of the neck that you take out?

Dr. SHANNON. The blood clots or hemorrhages in the substance of the brain or in the major vessels leading into or out of the brain. They all cause the same net results in doing major brain damage. While a great deal has been done about patients, and while a great deal now is done about some of the factors that lead to this, this is still a very obscure question from the standpoint of prevention of the occurrence of the thing and the major advance, as Dr. Knutti pointed out, is on the one hand ability to get them back to work—

Mr. DENTON. The main thing is to operate on them before the damage is done.

Dr. KNUTTI. There have been some techniques developed whereby it may be possible to diagnose ahead of time what may be happening in some of these vessels before they actually close off. There have been some very interesting instruments under development to see if one can measure the degree of narrowing of one of these vessels before they actually thrombose or close off. We are looking forward to this development with a great deal of interest.

Mr. FOGARTY. You have X-rays.

Dr. SHANNON. We have visualized them by radiopaque material.

ANTICOAGULANTS

Mr. FOGARTY. You spoke a little about anticoagulants but you did not say much about what you are doing or what progress has been made in anticoagulants. Do you want to say something about that?

Dr. KNUTTI. There is little doubt that the anticoagulant drugs have saved lives and have been very helpful following an acute attack of coronary thrombosis and they have been used extensively. The subject at the present time, however, is bound up in some controversy concerning the use of anticoagulant therapy as a preventive measure and there are wide differences of opinion among the experts as to whether anticoagulant drugs should or should not be used in individuals you might suspect of having an ultimate coronary attack. There has been a reopening of the whole subject because of the fact that it has become controversial. We have, sir, a special report on this subject that we would be happy to submit for the record.

Mr. FOGARTY. Put it in the record.

(The report follows:)

SPECIAL REPORT: ANTICOAGULANTS

Life—in organisms, their component organs, tissues and cells—depends upon the maintenance of blood fluidity and flow within the confines of the circulatory system. The vital nature of this system is reflected in the fact that no living cell has the temerity to reside further than 0.005 inch away from its blood supply, lest it die of starvation or drown in its own excretions.

In the higher animals and man, elaborate mechanisms have evolved that, on the one hand, maintain the fluid, functional state of blood, and on the other hand, make possible its transformation into the gel state (blood coagulation or thrombosis) to help stanch bleeding and hasten the healing of injured blood vessels.

Because the forces exerted by these procoagulant and anticoagulant mechanisms (involving a galaxy of factors occurring in blood cells, platelets, plasma, and tissues) are normally in a state of dynamic equilibrium, excessive inhibition or a deficiency of one or more of the factors involved can shift this equilibrium, thereby compromising the functional integrity of the circulatory system and of life itself.

Suppression or lack of natural coagulation factor(s) can be manifested in bleeding tendencies or overt hemorrhagic disease, such as hemophilia. Suppression of anticoagulant and/or clot dissolving (fibrinolytic) factors can result in the formation of a thrombus (blood clot) that may obstruct the blood vessel, or that may break away (embolize) and lodge elsewhere.

Thrombosis and thrombo-embolism cause or complicate the course of a formidable number of diseases, including thrombophlebitis, certain kinds of strokes, and pulmonary embolism. They are frequent complications of atherosclerosis and coronary heart disease, and are largely responsible for the crippling and lethal consequences of these diseases. Many scientists believe that blood clots may also contribute importantly to the early development of these diseases.

For the treatment of patients with impending or overt thrombo-embolic disease, two broad categories of therapeutic agents are available: (1) fibrinolytic

agents that dissolve blood clots directly, or that activate certain blood enzymes to do the job; and (2) anticoagulant drugs and other measures designed to prevent clots from forming in the first place. The anticoagulants—kinds, mechanisms of action, therapeutic effectiveness, and recent research—form the basis of this report.

The two most widely used types of anticoagulants are heparin and the coumarin derivatives or related compounds. Both suppress the fibrin clotting system (one of several clotting systems), but each accomplishes this in a different way.

Heparin, discovered in 1916, is found in various tissues of the body, particularly the liver and lung. Used clinically since 1938, heparin is a "direct" anticoagulant: it prevents the conversion of fibrinogen to fibrin, which is the structural substance of whole-blood clots. It acts by inhibiting thrombin, the blood enzyme that catalyzes this conversion. Because heparin has no effect when taken orally, it must be administered by injection. It is essentially nontoxic, does not interfere significantly with the healing of wounds, and its anticoagulant action can be promptly halted by injecting an equivalent amount of protamine sulfate.

The coumarin derivatives and related compounds are "indirect" anticoagulants. Unlike heparin, which inhibits the activity of thrombin, these drugs inhibit the formation of thrombin from prothrombin by reducing plasma concentrations of certain enzymes and precursors needed in the process. For this reason they are generally designated as "prothrombinopenic" drugs.

A hemorrhagic disease of cattle, sweet clover disease, in which the feeding of improperly cured hay was implicated as the cause, led in 1933 after years of research, to isolation of the causative agent. This was bishydroxycoumarin, destined to become one of the most widely used anticoagulants. More than a hundred chemically related compounds have since been studied, but only 11 have proved to be safe for clinical use.

Aside from bleeding, which is the most serious potential hazard of anticoagulation therapy, toxic reactions to these drugs are rare. Nevertheless, frequent examinations and laboratory tests are necessary to detect signs of drug toxicity and excessive depression of clotting factors. The effects of coumarin-type drugs can be reversed by administering vitamin K or by transfusing whole blood.

In addition to the fibrin-clotting system, at least two other mechanisms are known to effect clotting within the bloodstream. One acts through nerve and hormonal factors affecting blood-vessel permeability, fragility, and constriction. The other acts through the agglutination (clumping) of blood platelets and white blood cells, which organize to form white thrombi. These may, in turn, stimulate the fibrin-clotting (red thrombus) system.

These three systems may be equally important in hemostasis. Animals receiving anticoagulants and subjected to various types of stress—frostbite, insulin convulsions, adrenalectomy, and others—suffered a high mortality from spontaneous internal hemorrhage. The experiments showed that hemorrhage occurred when any two of the three mechanisms were deranged simultaneously. The results thus offer an explanation of the occurrence of certain unexpected and unexplained bleeding episodes during anticoagulant therapy in humans. They also provide a model against which to screen prospective anticoagulant agents for their ability to modify this reaction in animals.

CLINICAL APPLICATIONS OF ANTICOAGULANTS

The earlier unrestrained optimism concerning the use of anticoagulants both as therapeutic and as prophylactic measures in coronary heart disease has waned somewhat during recent months.

A large number of earlier reports had indicated that anticoagulants reduced the extent of heart-muscle damage and substantially increased survival rates when used during the acute phase of heart attacks. Others indicated that anticoagulants, used as a prophylactic measure, reduced the incidence of first heart attacks in patients with angina pectoris and of recurrent heart attacks among patients who had previously suffered myocardial infarctions.

In a number of recently reported studies, the benefits attending the use of anticoagulants in the treatment and prevention of heart attacks have been less spectacular. Some investigators have noted no significant differences in mortality rates between heart attack patients who were treated with anti-

coagulants and those who were not. Others have reported that anticoagulants appeared to be generally ineffective at heading off first heart attacks in patients with angina pectoris.

But perhaps the greatest controversy now rages around the long-term use of anticoagulants as a prophylactic measure against recurrent heart attacks. Some long-term studies have indicated that anticoagulants neither noticeably increase long-term survival after first attacks nor do they significantly reduce the incidence of recurrent attacks. According to the findings of certain of these investigators, the patient derives little benefit from such therapy. On the other hand, complications of therapy are common, though seldom serious. Further, the reduced coagulability state induced by anticoagulants has its dangers for the ambulatory patient going about his business. Industrial accidents, automobile accidents, and other bodily injuries are far more likely to entail serious or fatal consequences in such patients.

At present, there is no dispute concerning the effectiveness of anticoagulants in the treatment and prevention of certain disorders; venous thrombosis, thrombophlebitis, pulmonary embolism, cerebral embolism, and incipient or progressive strokes. Further, there is evidence to indicate that anticoagulants are beneficial in treating heart attacks in "high-risk" patients.

The value of anticoagulants in the treatment of heart attacks in "low-risk" patients and of long-term anticoagulant therapy to prevent initial heart attacks or recurrences is still a matter of controversy.

On one matter, there is near unanimous agreement: more objective, carefully controlled studies are needed for the accurate assessment of the clinical value of both long-term and short-term anticoagulant therapy in coronary heart disease.

This controversy, at least as it pertains to the acute and convalescent stages of myocardial infarction, may be resolved upon completion of a collaborative study now in progress. The study involves 16 medical institutions and about 1,000 patients. Incomplete returns from four Philadelphia hospitals indicate that anticoagulants, especially the prothrombinopenic drugs, are of definite value in reducing mortality during the acute and convalescent periods. These studies also show that wide variations in prothrombin activity depression resulted in only slight differences in mortality rates among those patients receiving prothrombinopenic drugs. If confirmed, this finding indicates that smaller doses of these drugs may be used to lessen the risk of hemorrhagic complications without jeopardizing effective anticoagulation.

OTHER FINDINGS BY NHI GRANTEES

A new clotting substance was recently detected in bovine and human aortas, extracted, and purified. Called *vasculokinase*, the substance is able to convert fibrinogen into fibrin *in vitro* independently of thrombin. Studies on the characteristics of this compound, including its indifference to the action of antithrombin, have established that it is an enzyme separate from thrombin or other proteolytic enzymes. The NIH grantees found evidence of significant *vasculokinase* concentrations in the aorta or in its direct branches, including the coronary arteries. There appeared to be some association between the concentration of this enzyme and the number and extent of atherosclerotic lesions. In later studies experimental atherosclerosis was induced in the aortas of animals within 10 weeks following the aortic injection of crude *vasculokinase*.

If future studies demonstrate an *in vivo* participation of *vasculokinase* in intravascular thrombus formation and/or atherosclerosis, the effects of anticoagulants on these must be evaluated.

In contrast to fibrin clot formation, platelet thrombosis is not observed in shed blood, in common test tube procedure, or *in vivo* under conditions of stasis, but is one of the most striking reactions to be seen in living blood vessels containing circulating blood. Initiated by vessel wall injury, the platelets agglutinate and form a thrombus which may grow until blood flow is stopped completely. A fibrin clot may then form in the stagnant blood.

Studies comparing the effectiveness of anticoagulants in preventing platelet versus fibrin clot formation in vessels of the hamster cheek pouch suggest that existing anticoagulant therapy provides potentially adequate protection against fibrin clot formation and thrombosis, but that present measures are probably inadequate to protect against platelet aggregation and thrombosis. In these studies, both heparin and coumarin compounds in usual doses prevented fibrin formation, but not platelet thrombi.

Recent grantee studies have demonstrated a unique platelet-inhibiting action of nialamide, a drug ordinarily used to treat mental depression. The drug also appeared to be more effective than the conventional coumarin anticoagulants, phenindione and warfarin, in preventing the development of intravascular clots.

The experiments involved three groups of rabbits: one received anticoagulants, the second received nialamide, the third received nothing. To stimulate clot formation, the inner walls of ear veins and arteries were then uniformly lacerated with a dental hand reamer.

This challenge produced a high incidence of intravascular blood clots in untreated control rabbits. Although test rabbits given large doses of phenindione or warfarin fared significantly better than untreated rabbits, by far the greatest antithrombotic effect was obtained in rabbits treated with nialamide. The scientists also found that subthreshold doses of nialamide and phenindione, given in combination, significantly reduced arterial thromboses, a synergistic effect that suggests a possibly useful method for clinical application.

Unlike phenindione or warfarin, nialamide had no direct effect on blood-clotting components involved in the conversion of fibrinogen to fibrin. Microscopic observations indicated instead that nialamide prevented the adhesion and aggregation of blood platelets and leukocytes at sites of vessel injury. Such aggregations, the scientists explain, constitute mechanical barriers that prevent the washing away of blood-borne clotting components of the fibrin system, as well as those released locally by injured tissue and disintegrating platelets. Thus the barriers initiate, indirectly, the formation of fibrin thromboses.

An as yet unnamed enzyme produced by *Pseudomonas* bacteria has been found to possess anticoagulant and fibrinolytic properties. In vitro and in vivo studies demonstrated a marked reduction of certain coagulation factors by this enzyme as well as a direct clot-dissolving action that does not involve activation of the body's own fibrinolytic system.

Many kinds of malignant tumors release cells into the bloodstream, especially when the primary tumor is manipulated, such as during surgery. Therefore, it has been postulated that characteristics of blood fluidity versus coagulation importantly affect the survival of released cells and the consequent development of secondary tumors in other parts of the body. Of particular interest are blood-clotting mechanisms that, during early stages of clot formation, cause increased stickiness and clumping of normal blood cells as well as of any tumor cells that may be present. Thus these mechanisms might influence the fixation and proliferation of wandering tumor cells into metastatic cancer.

NHI grantees have investigated the effects of anticoagulant drugs (heparin and warfarin), a clot-dissolving agent (human fibrinolysin), or a high fat diet on the survival and transplantability of circulating tumor cells and on the subsequent occurrence of metastases.

They found that rats treated with an anticoagulant or fibrinolysin developed significantly fewer metastases than did untreated rats, despite the fact that many tumor cells remained in the blood. Conversely, in rats whose blood was made coagulable, less lytic, or "fatty," there were increased numbers of metastases, and fewer circulating tumor cells.

The findings suggest that clinical trials of anticoagulant and fibrinolytic therapy are warranted for certain carcinomas that metastasize via the blood stream, including cancer of the lung and many sarcomas.

These studies will be extended to include combinations of anticoagulants, chemotherapeutic agents, and radiation, in the hope that further increases in antimetastasis can be achieved.

STROKES AND CEREBROVASCULAR DISEASE

Mr. FOGARTY. Also on strokes, I wish you would enlarge for the record on what is being done in that area. There are many people who do not think we are doing enough in this area of strokes. Will you expand on that in the record?

Dr. KNUTT. Yes.

(The information follows:)

NATIONAL HEART INSTITUTE ACTIVITIES IN STROKES AND CEREBROVASCULAR DISEASE

Cerebrovascular disease, including strokes, is a medical problem of much interest to the National Heart Institute since it is brain disease in which the blood vessels are heavily involved. Much of the research supported by the Institute in the fields of arteriosclerosis and hypertension thus relates to cerebrovascular disease. In addition, a number of investigations are directly concerned with specific aspects of the problem. Encouraging research developments were reported from several of these during the year.

A new method for measuring cerebral circulation time has been devised by Heart Institute grantees and successfully tested in a glass model and in specially prepared dogs. In this method, which uses I^{131} labeled albumin injected intravenously, a radiation monitor over the brain records a curve which resembles but differs from a curve simultaneously obtained of the time course of radioactivity in inflowing arterial blood. The dog studies have established that differences in the contours of these curves are quantitatively related to the time it takes for blood to circulate through the brain. If the method proves applicable to man, the circulation times in different parts of the brain could be measured and compared.

Initial reports on the use in cerebral angiography of a promising new radiographic contrast agent were made by a Heart Institute grantee during the year. Laboratory and preliminary clinical trials showed that visualization of carotid and vertebral arteries with the contrast medium was excellent and side effects were found to be less than anticipated on the basis of experience with other agents.

Since cerebral arterial insufficiency due to impeded blood flow in extracranial arteries supplying the brain can be averted in many instances by medical and surgical treatment, the need exists for diagnosing blockage of such arteries in routine physical examination before cerebral damage occurs. In a study undertaken to evaluate the usefulness for such diagnosis of systematic auscultation with a stethoscope, a group of 50 patients with cerebrovascular disease were studied by auscultation of the major extracranial vessels in the neck with the head turning and the results were compared with findings obtained by arteriography. Auscultation of the neck carotid arteries led to detection of 57 percent of atherosclerotic plaques and auscultation of the neck vertebral arteries led to detection of about 45 percent of atherosclerotic plaques shown by arteriography.

Data continued to be accumulated in the collaborative study of extracranial arterial occlusion in which some 24 investigative teams are currently participating. In this joint study, patients with symptoms of cerebral arterial insufficiency are being studied by angiography and other diagnostic techniques to determine the importance of blocked blood flow in extracranial arteries supplying the brain as a primary cause of the symptoms. Those with occluded arteries who are judged likely to benefit from surgery are operated upon to remove or bypass the obstruction to blood flow. Data from the participating teams are being pooled in a central registry. Among results from the study may be better criteria for selecting patients for surgery and for determining the optimum form of treatment.

A review by an outstanding investigative team of its experience with surgical treatment of occluded extracranial arteries located in the neck and upper chest showed most gratifying results in restoring blood flow and relieving cerebral arterial insufficiency. Of 382 patients with neurological disturbances, 93 percent survived operation. Symptoms were relieved immediately in 85 percent of those with transient cerebral blood insufficiency, in 80 percent of those with progressing strokes, and in 56 percent of those with completed strokes. Followup observations, ranging from eight months to eight years after operation, were impressive. Relief of symptoms had been maintained in 90 percent of patients with transient cerebral insufficiency, in 96 percent of those with progressing stroke, and 69 percent of those with completed stroke.

In another grant-aided investigation, the effect of hypothermia in cerebral blood insufficiency was studied in the dog. The cerebral blood insufficiency or ischemia was produced by a technique involving cuff compression of the neck, cutting off all circulation to the brain. Brain hypothermia or cooling was accomplished by a technique in which removed arterial blood is cooled and returned to the animal through the carotid arteries. In these animal experiments it was

found that the dog will tolerate total cerebral ischemia for 8 minutes at 37° C., 25 minutes at 28° to 30° C., and 60 minutes at 19° to 21° C. without evidence of permanent brain damage. The technique of selective brain cooling developed by the investigators has already been successfully performed in two patients. One was a woman with a tumor in the area of the right mastoid and middle ear. Because of its location and vascularity, the tumor was not operable unless its total blood supply could be stopped during an anticipated 20 to 40 minutes that might be required for removal. The brain was cooled to about 20° C. and the tumor removed in about 10 minutes in a dry field. In the second instance, the brain of a woman with an intermittently bleeding aneurysm of the posterior communicating artery was selectively cooled to 6° C. and blood flow cut off. Circulation to the brain was stopped for 30 minutes while the aneurysm was clipped. The investigators report that neither patient has shown evidence of brain damage from either the brain cooling or the period of total cerebral ischemia.

DEVELOPMENT IN BIOENGINEERING

Mr. FOGARTY. What are you doing in bioengineering?

Dr. KNUTT. There have been some very interesting developments in the field of bioengineering which have been taking place over the past few years. One of the first of these was the development of the intricate pumps that are used in open-heart surgery. Other developments which are now in use are special flowmeters which can be embedded in the walls of vessels in order to measure the rate of blood flow and therefore the volume of blood flow passing through these vessels. This has been very actively studied and there are further developments going on in this respect, both at the NIH and in some of our grantee institutions. Some developments have been taking place in the attempt to relieve the work on the left side of the heart, which does the pumping of the blood through the arteries over the body, by inserting a cannula in the aorta and simultaneously with the heart-beat, to pump off the blood and reinject it into the big leg artery. This has been very helpful in some individuals who needed all of the strength in the heart they have to keep going.

Another thing in which we have been particularly interested, and which I heard Dr. Lillehei talk about just 2 weeks ago at a meeting in Los Angeles, is the actual development of a mechanical heart. The planning committee of the National Advisory Heart Council has been consulted on the feasibility of such a project. The staff and I have talked with some of the experts in this field, including Dr. Lillehei. There seems to be a consensus that we have the basic know-how at the present time to push forward with the study of the implementation of the actual development of an artificial heart. This is as far as we have gone because these discussions have taken place over the past 2 or 3 months. But we have been asked by the Council to form an expert committee to recommend to the staff and to the Council ways and means to implement plans for a big developmental approach to the artificial heart.

FRAMINGHAM FINDINGS ON HEART ATTACK PRONE INDIVIDUALS

Mr. FOGARTY. Can anybody predict a heart attack?

Dr. KNUTT. Not in most instances.

We have certain criteria that have been developed as to the heart attack prone type of individual which has come out of the Framingham studies and other studies.

Mr. FOGARTY. Put that in the record, will you?

(The information follows:)

THE FRAMINGHAM STUDY

The Framingham study represents the "microscopic" approach to the epidemiological study of coronary heart disease. This involves the intensive study of a relatively small group to detect within-group differences in the incidence of the disease and to discover factors within the host or his environment that appear to be responsible for these differences. These risk factors and their relative importance in the development of CHD are then assessed in long-term studies on subjects initially free from the disease. The aim is to determine whether the presence of one or more of these factors in members of the population significantly affects the subsequent development of the disease in these members.

Carefully controlled studies on 5,128 adults, found to be free from heart disease at initial examination and followed for periods of 8 to 12 years, indicate that the following factors are important determinants of susceptibility to heart disease.

Age and sex.—In both men and women, the incidence of CHD rises sharply with age. Men tend to develop the disease at an earlier age than do women, who enjoy about a 10-year lag in the development of angina pectoris and a 20-year lag in the development of heart attacks. This "grace period" enjoyed by the women may be due to the protective action exerted by estrogenic hormones during their reproductive years.

Men also tended to develop more lethal forms of coronary heart disease. In approximately 70 percent of the males, the first clinical manifestation of the disease was myocardial infarction ("heart attack") or sudden unexpected death. In about 70 percent of the women, it became clinically manifest as angina pectoris. These findings suggest that a major sex difference in CHD may lie in the male's greater proneness to complications involving blood clots.

Elevated serum cholesterol.—The risk of developing coronary heart disease increased progressively with elevations in serum cholesterol levels: the higher the serum cholesterol, the greater the risk. The effect of elevated serum cholesterol levels on the development of heart disease was greater in young men than in older men. In young men with serum cholesterol levels higher than 260-milligrams percent the risk was approximately six times that of subjects whose levels were lower than 220-milligrams percent, the average value for adult males at Framingham. This and other observations suggest that atherosclerosis may be related both to the elevation of serum cholesterol and to the time during which that elevation is present.

Elevated blood pressure.—In both men and women, there was an increasing gradient of risk with increased blood pressure; the higher the blood pressure, the greater the risk. This gradient of risk appeared to apply even in the so-called normal range of blood pressure. In going from systolic blood pressures of less than 120 to pressures exceeding 180, there was a sevenfold increase in risk.

Electrocardiographic (EKG) changes.—Certain EKG changes not usually considered indicative of coronary heart disease nevertheless appear to identify susceptible persons. Changes indicative of left ventricular enlargement or non-specific abnormalities appear to double the risk of developing CHD.

Cigarette smoking.—Cigarette smoking more than doubled the risk of developing the severer forms of coronary heart disease, such as myocardial infarction, but did not increase the risk of developing angina pectoris. The risk of myocardial infarction appeared to increase with the intensity and duration of exposure to cigarette smoking. Persons who smoked pipes or cigars appeared to run no greater risk than did nonsmokers. A happy note was provided by the finding that persons who had given up smoking ran no greater risk than did those who had never smoked. This finding suggests that cigarettes may not contribute materially to the development of atherosclerosis itself, but might help to trigger certain of its lethal complications, such as thrombosis or fibrillation.

Obesity.—Men or women with weights 30 percent or more above the median weight for their height and sex double their risk of developing heart disease. The higher risk appears to be due primarily to elevations in blood pressure commonly associated with overweight.

The risk of developing coronary heart disease may be greatly increased in individuals with combinations of the above risk factors. Fortunately, few individuals have all of these factors working against them; but a goodly number may have combinations of two or more. A combination of only three—elevated

blood pressure, elevated serum cholesterol, and EKG abnormalities—may increase an individual's risk by a factor of 25. Fortunately, many of them can be eliminated with the aid of the physician.

Dietary factors.—Epidemiological studies have provided an overwhelming mass of statistical evidence linking the kinds and amounts of fat in the diet to elevated serum cholesterol levels, the factor most consistently associated with increased susceptibility to atherosclerosis and coronary heart disease. In general, this evidence indicates that serum cholesterol levels tend to be elevated by diets high in total fat, with a preponderance of these fat calories in the form of saturated fats. Conversely, serum cholesterol levels are usually lowered by diets containing less total fat, with a preponderance of these fat calories in the form of unsaturated fats derived from certain vegetable or marine oils. Although it is not yet clear how unsaturated fats reduce serum cholesterol levels, there does appear to be a definite correlation between the degree of unsaturation of any given fatty acid and its cholesterol-lowering properties: the more highly unsaturated the fat, the greater its reduction of serum cholesterol.

The findings of many epidemiological studies indicate that, except for very special groups within the United States (such as Trappists, Seventh-day Adventists), most Americans habitually consume a diet high in calories, total fat, and saturated fat. These findings suggest that this prevailing dietary pattern may be responsible in large measure for our very high death rate from heart disease. If this is the case, it might well be possible to bring about a significant reduction in mortality from heart disease through modifications in this dietary pattern. However, to prove or disprove this attractive hypothesis would require long-term population studies on a scale never before attempted.

With NHI grant support, a committee of experts has studied the many problems inherent in a massive undertaking of this sort. These investigators have concluded that before long-term, large-scale population studies can be undertaken with any success, the feasibility of such studies should be carefully tested.

This will be done by means of a series of short-term studies in small population groups, composed mainly of free-living, middle-aged American males. Each group will consist of at least 225 men. They will be evenly divided into three populations and fed three separate diets. These diets will differ in their content of saturated, polyunsaturated, and total fat calories. The investigators will carry out various clinical and biochemical studies to evaluate the effects of these diets on certain factors associated with increased coronary disease risk and also on the development of the disease itself.

Metabolic disorders.—Susceptibility to coronary heart disease is increased by certain metabolic disorders, among them hypercholesterolemia, hypothyroidism, and diabetes. The elevated serum cholesterol levels resulting from hypercholesterolemia and hypothyroidism appear to be directly responsible for the increased risk of heart disease attending these disorders. Diabetes is accompanied by atherosclerosis and other vascular complications, and coronary heart disease is a leading cause of death among diabetics; however, the factor or factors responsible for the cardiovascular complications of the disease are not clear.

Occupation and degree of physical activity.—The results of many epidemiological studies indicate that heart disease is more prevalent among workers engaged in sedentary jobs than in those whose jobs entail moderate or marked physical exertion. Further evidence supporting this concept has come from studies on the incidence of heart attacks occurring over a 10-year period among 8,500 middle-aged workers in Israel cooperative settlements. In these settlements, all members live in absolute equality with respect to housing, nutrition, and other environmental factors, irrespective of the nature or status of work performed.

The study showed that heart attacks were three times as common among the sedentary workers of these settlements as among those engaged in light or heavy manual labor. Other evidence collected by the same research team suggests that not only does physical labor confer some measure of protection against the development of heart disease, but it also appears to exert a favorable effect on both immediate and long-term survival after first heart attacks.

Stress.—The fact that psychic stress can produce striking elevations in serum levels of cholesterol and other lipids has been demonstrated in many studies. Considerably less is known concerning the role, if any, played by stress in the development of coronary heart disease.

Whenever stress and heart disease are mentioned together, most people conjure up an image of a hard-driving, high-strung, ambitious, and aggressive

Madison Avenue executive collapsing over his paperwork from coronary occlusion. The clinical impressions of many doctors is that such high-pressure types are prone to heart disease.

Evidence supporting this concept that high-tension living is related to increased susceptibility to coronary heart disease is provided by studies comparing groups of subjects exhibiting two distinct types of behavior pattern. One group was characterized by excessive competitive drive, a persistent desire for recognition and achievement, chronic immersion in "deadline," and other characteristics frequently attributed to the high-pressure executive type. The other group was selected on the basis of entirely opposite behavioral traits. Comparison of these two groups indicated that males exhibiting the aggressive behavior pattern had much higher serum cholesterol levels, more rapid blood-clotting times, and a sevenfold higher incidence of heart disease than did the easygoing group.

The female executive type fared little better than her male counterpart when studies were conducted on two groups of women selected on the basis of these two behavioral patterns. The aggressive group exhibited markedly higher serum cholesterol levels, more rapid blood-clotting times, three to seven times more diastolic hypertension, and four times as much clinical heart disease as did their more placid sisters.

Geographic location.—Although mortality from coronary heart disease is generally high throughout the United States, striking variations in coronary heart disease mortality exist in different regions, States, and metropolitan areas. For example, the coronary heart disease mortality rate of New York is more than twice that of New Mexico. Racial, dietary, or social differences do not appear to account for these differences in coronary heart disease mortality.

A recent study correlated death rates by State with drinking water, an environmental influence affecting all persons. Significant correlations were found between death rates from coronary heart disease and water hardness. States, regions, or cities with hard water tended to have lower mortality rates from coronary heart disease than did those with soft water.

These significant correlations persisted when these data were applied to various constituents contributing to water hardness, such as its content of magnesium, calcium, bicarbonate, sulfate, fluoride, silica, and total solids. The findings suggested that hard water might contain something that is beneficial to the outcome of cardiovascular disease, or soft water something harmful. It appeared unlikely that soft water should lead to a deficiency of calcium, magnesium, or other essential minerals, since these are supplied largely by the diet.

Another possibility being explored in a number of studies is that the presence or absence of certain trace metals, such as lead, cadmium, mercury, vanadium, and many others, might account for the differences in coronary heart disease mortality associated with differing degrees of water hardness. Very little is known about the effects of many of these metals on the body and its metabolism. Until much more is known, the riddle posed by the relationship between water hardness and coronary heart disease is likely to remain unsolved.

The evidence gained from epidemiological studies conducted thus far indicates that the development of atherosclerosis and coronary heart disease is influenced by a whole constellation of factors. Presently underway in Michigan is an ambitious, long-term project which proposes to examine a wide variety of these factors, to relate them to biochemical and physiological processes, to study their interrelationships, and to assess their individual and collective influence on the development of cardiovascular disease within the framework of an entire community.

INTERNATIONAL RESEARCH

Mr. FOGARTY. What are you doing in the field of international research?

Dr. KNUTT. In addition to the geographic pathology that I described earlier, we are supporting rather broad research in the cardiovascular area in a number of countries in the world. I cannot give you the breakdown on that now, sir, but I would be glad to supply that for the record.

Mr. FOGARTY. All right.

(The information follows:)

Research grant support for international research, estimate of support for 1963

Country	Number of grants	Estimated amount	Country	Number of grants	Estimated amount
Argentina.....	5	\$51,963	Japan.....	16	\$143,189
Australia.....	6	157,757	Korea.....	1	5,405
Austria.....	3	30,713	Lebanon.....	2	30,147
Belgium.....	3	49,160	Mexico.....	3	51,075
Brazil.....	6	90,472	Netherlands.....	8	104,133
Canada.....	27	526,076	New Zealand.....	2	30,910
Chile.....	2	18,040	Peru.....	5	97,303
Colombia.....	1	1,800	Philippines.....	1	8,450
El Salvador.....	1	25,070	South Africa.....	5	93,529
Finland.....	2	21,500	Sweden.....	15	272,311
France.....	5	54,740	Switzerland.....	2	19,956
Germany.....	1	6,720	United Kingdom.....	18	354,645
Greece.....	2	16,850	Uruguay.....	1	39,615
Guatemala.....	1	52,012	Venezuela.....	1	35,806
India.....	1	7,700	Yugoslavia.....	1	10,500
Ireland.....	1	15,985			
Israel.....	10	214,524	Total.....	164	2,729,096
Italy.....	6	89,035			

RELATIONSHIP OF DIET TO HEALTH

Mr. LESINSKI. Dr. Knutti, there seems to be a lot of to do about cholesterol in the last few years and I read an editorial back in about 1935 where cholesterol was considered to induce heart trouble and so forth and ever since then I have cut down my animal fats and I am happy I did.

You mentioned in your statement animal fats and oils and vegetable oils. Would there be a difference between a mammal such as the whale and seal?

Would the mammal have cholesterol in it?

Dr. KNUTTI. The whale or the seal or other aquatic mammals would have cholesterol, but their fat would be different from other mammals in that the fatty acids would be unsaturated.

Mr. LESINSKI. The cod would not?

Dr. KNUTTI. The cod would be the same, but except in the liver it has very little body fat.

Mr. LESINSKI. You mentioned the study of Chinese in relation to heart attacks and various types. Is it pellagra or beri-beri?

Dr. KNUTTI. Beri-beri.

Mr. LESINSKI. You went into the matter of diets of the Japanese which is mostly fish and the Chinese was mostly rice.

Have you taken into consideration the differences between polished and unhulled rice?

Dr. KNUTTI. That is an interesting question. Because just recently there have been some studies done in East Pakistan relative to the possibility of vitamin B₁ deficiency in the natives. They have found out that in patients who have cholera, the electrocardiogram gives the same type of tracing that the electrocardiogram gives in beri-beri which is the vitamin B₁ deficiency disease which is associated with heart failure.

So far as is known, the rice that is consumed, and this is just about the principal source of their diet in East Pakistan, the rice that is

consumed there, is not polished down to the point where it is deficient in vitamin B₁.

Mr. LESINSKI. But it is polished to a certain degree.

Dr. KNUTTI. The rice you get in the restaurants is polished. There seems to be enough vitamin B₁ in the rice or in other things they eat to protect them from B₁ deficiency. On the other hand, these same natives of East Pakistan, when they get cholera, exhibit signs of vitamin B₁ deficiency as far as their heart tracing is concerned.

Mr. LESINSKI. There might be a definite bearing between your heart failure and deficiency in vitamin B₁.

Dr. KNUTTI. Yes, sir.

Mr. LESINSKI. Actually heart failure evidently from what you have declared here and from my personal knowledge, is a combination of diet and the type of work you do, your well-being, environment, et cetera, which all has an effect upon the health of your heart.

In other words, tension, strain, excessive indulgence in some things, et cetera, all of this has a bearing upon it, right?

Dr. KNUTTI. Yes, sir, and one thing that I did neglect to mention that is of importance is the genetics of coronary disease or atherosclerotic disease.

We have the clinical impression that there are families in which the men consistently die at quite young ages of coronaries and whether or not this is a genetic trait is something that is extremely important to study.

We have a hunch that this accounts for one type of the disease. I know of no conclusive study that has been done to prove this. But this is one of the things that we are paying very definite attention to in the studies that are being developed.

Mr. LESINSKI. My father died at the age of 65 of a heart attack, May 27, 1950. An aunt of mine went to a doctor for a physical, nothing was wrong with her, he put her on a cholesterol-free diet. In 2 months she had a heart attack. The doctor put her right back on the original diet. By withdrawing cholesterol which normally she was used to in her diet and by restricting it, it did more harm than good.

PRODUCTION OF CHOLESTEROL

One further question, Is not cholesterol necessary for the development of the brain?

Dr. KNUTTI. Yes, sir, it is necessary for the activity of the brain and actually there is a certain amount of cholesterol that is made by the brain itself.

Mr. LESINSKI. By the brain itself?

Dr. KNUTTI. Yes, sir.

Mr. LESINSKI. You also mentioned the fact that regardless of what you eat, the organs develop cholesterol in the body.

Dr. KNUTTI. Oh, yes; what I was attempting to point out was that the total source of our body cholesterol is not from the pure cholesterol that we eat, but from cholesterol that is synthesized by the liver from other substances that we eat but those other substances are not pure cholesterol.

Mr. LESINSKI. Have you any knowledge as to what those substances may be?

Dr. KNUTTI. Yes.

Mr. LESINSKI. What are they?

Mr. KNUTT. Cholesterol is synthesized from acetate and this is obtained by the breakdown in the metabolism of sugar, of protein, of fat—all three of our primary dietary substances may form acetate from which cholesterol can be synthesized.

BUDGET ADJUSTMENTS

Mr. DENTON. I just wanted to ask a couple of questions. I am having an awful time figuring this out.

At page 214, it shows for the 1963 appropriation \$147,398,000 and for 1964 it is \$133,624,000. Now that looks like you are spending quite a bit less this year than you did last. But the note says that you are supposed to take from this \$19,535,000 which was transferred to other agencies.

Mr. KELLY. Yes, sir.

Mr. DENTON. If you do that that would leave \$127,863,000 for 1963. Am I right about that?

Mr. KELLY. The amount of the footnote was \$19,535,000?

Mr. DENTON. Is that right?

Mr. KELLY. If you will look at page 2—

Mr. DENTON. I am coming to that. I looked at your justifications and I find you start out with 1963 at \$147,398,000 and \$133,624,000 for 1964. But this was transferred to other accounts and unobligated balances brought forward and other transfers. When you get through with that you have \$129,793,000 for 1963 and \$134,059,000 for 1964 which would show you will spend about \$4 million more in 1964 than last year. But then I look over on page 212 and you had an unobligated balance from 1962 that was carried over to 1963 which was \$12,177,000.

UNOBLIGATED BALANCE OF 1963 FUNDS

Mr. KELLY. The \$12,177,000 is part of the money which Congress made available for 1963 which we do not contemplate using, and expect to revert to the Treasury.

Mr. DENTON. That was money cut by Secretary Ribicoff?

Mr. KELLY. No, sir. That occurred in 1962. In the 1963 act, to the best of our knowledge and belief, there is \$12,177,000 we will not use; \$1,177,000 of it is in the apportionment reserve for savings and \$11 million is in the reserve for contingencies. It is this contingency that we do not anticipate receiving approvable projects that will require the funds, but have agreed that if we receive approvable projects that we will reconsider that reserve for contingencies.

Mr. DENTON. You mean this is money that was appropriated in 1963 which you are going to spend in 1964 if you have approvable projects?

Mr. KELLY. No, sir. These were put in the contingency on the assumption that \$12,177,000 was money that you made available for use in 1963 and which will not be used and this is what Dr. Terry talked about with the committee. One of the areas in which he felt we can be proud of our stewardship is that we have not utilized any of the funds that Congress made available unless we felt that there were programs of scientific excellence that justified their use.

ANTICOAGULANTS

Mr. DENTON. Just one last question.

You spoke, Doctor, about a drug that is used to dissolve blood clots.

Dr. KNUTTI. Yes, sir.

Mr. DENTON. I did not quite get the explanation. Did you tell how far we had gone with that?

We have had anticoagulants for some time. I understand you had something new that would dissolve a clot.

Dr. KNUTTI. There have been certain enzymes that have been known for some time to dissolve blood clots. There is no problem in dissolving blood clots when the clots are outside the body, in a test tube. The difficulties in dissolving them, when they are in the heart, in the coronary artery or in other vessels, rests in the possibility of upsetting the balance between the clotting factor and the nonclotting factors, which are in very delicate balance in the living person.

So you have to have some type of compound or enzyme that will attack the clot without upsetting the clotting, nonclotting balance that exists in the body.

There are some enzymes that have been tested out, that will do this in certain instances, like in the thrombophlebitis. This is a thrombosis of the veins.

The difficulty to date has been in getting uniformly pure substances. There has been a great deal of controversy among workers in the field about standardization of these substances. This is a very delicate process. It is also very difficult.

So the Heart Institute has set up a committee of consultants in this field, and these consultants comprise the very people in the field who have been involved in the difficulties. They are the top men in the field.

We hope, by getting them together, to work out reasonable means to attack this problem; so we can support good research, through grants, to ultimately find how one can go about to dissolve a clot after it has once been formed without having a bad effect on the rest of the body.

Mr. DENTON. Can you tell whether it is an embolism or whether it is calcium?

Dr. KNUTTI. We have not found anything yet that will dissolve calcium; but the embolus which is formed from the breaking off of a thrombus is also composed of this same blood clot material. An embolism comes from breaking off of a portion of the clot that is already present in the vessel.

Mr. DENTON. I think that is all.

Mr. FOGARTY. All right; is there anything else you would like to say, Doctor?

Dr. KNUTTI. Nothing, sir, except to say I would like to express my appreciation for the support the committee has given to our Institute.

Mr. FOGARTY. Thank you very much, Doctor.

SUMMARY STATEMENTS

We will place your special report on hemophilia and the usual statements on cost and research highlights in the record.

(The statements referred to follow:)

SPECIAL REPORT ON HEMOPHILIA

Introduction.—Stubbed toes, skinned knees, cut fingers, and a bruised head are just a part of growing up to most boys. To the hemophilic boy and his parents they are dreaded accidents, for they mean hospitalization, loss of blood, agonizing pain, repeated transfusions—maybe even death.

Hemophilia is an incurable hereditary bleeding disorder characterized by the absence of a certain plasma factor which is vital to the blood-clotting mechanism. Only males get the disease although females carry it. If a hemophiliac lives long enough to marry and have children, his sons and daughters will be normal. His sons' sons will be normal. His daughters, however, will carry the disease—through a sex-linked recessive gene—to her children. If she has boys, half of them—like their grandfather—will be hemophiliacs.

Better means of treating and caring for hemophiliacs have increased their average life span—from 14.5 to 29 years since 1940—to the point where some marry and raise families, passing the defect on to further generations. Today, there are about 40,000 known hemophiliacs in the United States.

So far, about 12 hereditary bleeding disorders—caused by a plasma deficiency of one sort or another—have been discovered. Hemophilia, types A and B, comprise about 90 percent of these disorders. Of this amount, about 16 percent are the B type.

Hemophilia A is characterized by the absence of the antihemophilic factor (AHF) found in normal plasma. This factor is also known as antihemophilic globulin (AFG), factor VIII, and platelet cofactor I.

Hemophilia B is characterized by the absence of another plasma factor, plasma thromboplastin component (PTC), known also as factor IX. This disorder is also known as PTC deficiency, and Christmas disease, named after a patient in whom it was first isolated.

Uncontrollable bleeding usually occurs early in the hemophiliac's life. One NHI grantee has reported that bleeding occurred in the first 10 days of life in 35 percent of the patients studied. Bleeding occurred at the umbilicus or in the brain, or resulted from circumcision. Bleeding in the joints occurred in 85 percent of the patients before they were 3 years old, the grantee said.

Hemophiliacs live in constant fear of injury. Those injuries which cause internal bleeding and bleeding into joint cavities are by far the most serious. A slight blow to the head may cause bleeding in and around the brain. A banged knee, suffered while simply getting up from the table, may cause extensive hemorrhaging into the knee joint cavity. Such bleeding can swell the knee to the size of a watermelon and the resulting pressure will cause excruciating pain. Repeated injury to a joint—especially if untreated—can cripple it, requiring the victim to wear braces. External bleeding, from small cuts, scrapes, and nosebleeds, is not as serious, thanks to improved methods of treatment.

Surgery on hemophiliacs continues to be a major problem, although better results have recently been reported.

The clotting process.—When blood coagulates, an unknown number of reactions occur, many factors participate, and many new agents are formed. The mechanism, though not fully understood, can be briefly outlined in three steps:

In the first step of the process, intrinsic thromboplastin is generated. A factor from the platelets and several constituents of the plasma participate in this step. These constituents are the antihemophilic factor (AHF), lacking in hemophilia A; plasma thromboplastin component (PTC), deficient in hemophilia B; and several other constituents which are less clearly defined.

The second step in the mechanism is the production of thrombin from prothrombin under the influence of intrinsic thromboplastin. The third step is the conversion of fibrinogen to fibrin (clot) by the catalytic action of the thrombin formed in the second step.

Diagnosis.—Diagnosis of hemophilia utilizes routine procedure. First the physician takes a complete medical history of the patient to determine if other members of the family were bleeders. Then he gives the patient a careful physical examination, taking into account bruises and other injuries that are slow to heal. Several established laboratory tests are used to make the final diagnosis.

Diagnosis of the mild form of hemophilia is much more difficult than the detection of the severe type. According to NHI grantees, many cases of mild hemophilia often go undetected until the victim undergoes surgery for some unrelated disorder. Surveys show that these cases of mild bleeders are far more prevalent than the severe ones.

Treatment.—There are three classifications of treatment for hemophilia: preventive, local, and systemic.

Preventive treatment, especially, should not be overlooked since the hemophiliac rarely bleeds spontaneously. Thus, the more he is protected from injury, the less chance he has of suffering a bleeding episode. Hemophilic boys have fewer bleeding episodes as they grow older since, after reaching a certain age, they learn to be more cautious.

Some hemophiliacs avoid analgesic drugs such as aspirin, claiming that they increase their bleeding tendency. Unfortunately, not enough controlled studies have been made to evaluate the effects of analgesics on bleeding.

Local methods of stopping the blood flow should be attempted first in treating a bleeding episode. The use of cold and pressure often brings excellent results. Blood vessels are constricted by cold, and the reduced blood pressure minimizes the bleeding. Topical preparations, applied directly to the injury, may also stop bleeding. Theoretically, thrombin should be the drug of choice. In practice, however, it has been found to be of little value. Other useful preparations are fibrin foam and gelatin sponge.

For extensive internal bleeding, the treatment of choice is blood transfusion. For hemophilia A, regular stored bank-blood is not satisfactory, since its AHF activity is lost shortly after removal from the donor. Therefore, plasma must come directly from a donor, or it must have been frozen immediately after withdrawal.

The use of fresh blood for transfusing into patients with hemophilia B (PTC deficiency) is not as important. Heart Institute grantees have recently shown that plasma prepared from outdated bank blood retains its PTC activity. The investigators checked the influence of stored plasma on the PTC level of a patient born with severe PTC deficiency.

From time to time, many procedures and drugs have been advocated as having curative effects in hemophilia. The idea of splenectomy was a recent vogue, for example. A thorough study of the effects on clotting by removing the spleen have shown this radical form of therapy to be of little beneficial value.

For several years, it was thought that if the hemophiliac ate foods with a high fat content, his blood would more readily clot. A grant supported study has shown this theory to be false.

Other research on hemophilia.—One of the most noteworthy advances in the care of the hemophiliac seen in this country in recent years is the development and clinical use of a highly concentrated form of AHF.

Until recently, most hemophiliacs were out of luck if they needed an operation. Of those who underwent surgery, 25 percent died. The new AHF plasma concentrate has completely changed this picture. Now, a hemophiliac can undergo surgery and expect to have almost the same chance for survival as persons without the disorder.

The Fraction I concentrate, rich in antihemophilic factor, is being commercially produced in this country only by Merck Sharpe & Dohme. It is transfused into the patient before surgery, temporarily normalizing his plasma AHF. Results have been excellent since clinical use of the concentrate was first reported in the United States by Boston investigators in 1961. Employing an established alcohol sedimentation technique in its production, the concentrate has been used successfully in Denmark, England, Sweden, Australia, and Switzerland for almost 10 years. A lack of money slowed its full development and use in this country.

The lifesaving therapy is far beyond the reach of most hemophilic families. Plasma concentrate sufficient for one operation—150 to 800 grams—can cost from \$2,500 to \$5,000, and occasionally \$10,000. Six hundred donors must give their blood in order to obtain enough Fraction I AHF concentrate for an average treatment.

Much more research is needed to simplify the fractioning process and reduce the price of the concentrate to a level within reach of any hemophiliac needing surgery. Right now, scientists in the National Institute of Arthritis and Metabolic Diseases are studying the best therapeutic use of the Fraction I AHF concentrate in surgical cases and in the more severe complications of hemophilia.

This involves determining how long the factor survives in the body, where it localizes in the body, and its period of effectiveness.

Better ways of concentrating and assaying the factor are under study. The Arthritis Institute scientists have developed an assay method to detect relatively small amounts of antihemophilic factor within the body. This new method provides a basis for developing better therapeutic regimens with the antihemophilic agents currently available, and it will permit easier evaluation of new agents.

Investigators in Buenos Aires, Argentina, have also been working with the purification of AHF. Using the standard alcohol sedimentation technique, they obtained an AHF-rich Fraction I concentrate. Then they used tannic acid and precipitated out the fibrinogen, thus obtaining a much purer fraction of factor VIII, which they termed FI-O-Ta.

The Argentine scientists reported excellent results in the clinical use of FI-O-Ta. One patient—unable to walk for 3 years because of bleeding in his right knee joint—recovered normal function in his knee after 27 injections of the concentrate.

Two years ago, several of these Argentine scientists were working at the National Cancer Institute as visiting scientists. During this time, they, in collaboration with National Cancer Institute scientists, developed an experimental method for isolating the antihemophilic factor in an even purer form.

Their purification process utilized a chromatographic technique instead of the standard alcohol sedimentation method. The AHF concentrate obtained with chromatography was purer than the AHF concentrates obtained from conventional processes. Furthermore, the investigators found they could obtain a highly purified fraction right from diluted plasma without resorting to preliminary purification—a distinct advantage.

A research foundation in New England, currently being supported by NIH, is also investigating the application of chromatographic techniques in combination with other standard methods for the purification of human plasma proteins for the preparation and eventual characterization of purified AHF. Although clinical testing of the concentrate has started, results have not yet been reported.

Meanwhile, scientists in the Division of Biologics Standards are trying to achieve some means of standardizing the various Fraction I AHF concentrates so that consistent results may be obtained in clinical use.

An NHI grantee in Boston has found that flavinoids, found in "cold cures" may reduce the severity of bleeding episodes by as much as 50 percent. He has been careful to state, however, that his results, though dramatic, are not conclusive, since he studied the effects of flavinoids in only six hemophiliacs over a 6 year period.

The first year, the six patients received a placebo. The second year, they were given several flavinoids, and the incidence of their bleeding episodes and the number of transfusions went down 50 percent. The third year was a placebo year and the incidence of bleeding episodes went back to its original level. In the fourth year, the patients received one flavinoid, prednisone, and the bleeding episodes again decreased 50 percent. The incidence went back up when placebos were administered in the fifth year. The sixth year, the investigator gave the patients another specific flavinoid, dexamethasone, and the levels again went down 50 percent. Not only did the incidence decrease during the even-numbered years, but the nature of the bleeding episodes changed. There was less bleeding within joints and internal structures.

The changes in the bleeding episodes were not reflected in measurements of the blood clotting factors. The Boston investigator is not yet sure of the exact mechanism of change. One possibility he says, is that the flavinoids increase the acid mucopolysaccharides in blood vessels, thus increasing their strength.

Another area of research which needs strengthening is the epidemiological study of hemophilia. There is much work to be done before all hemophiliacs in this country are located and diagnosed. Sweden, for example, has a complete record of each of its hemophiliacs, including family histories.

There have been reports recently of circulating anticoagulants in the blood of hemophiliacs. One NHI grantee, in studying the antihemophilic factor, has found that the inactivation of AHF by circulating anticoagulants is enzymatic in nature and may be a kind of antigen-antibody response. Hemophiliacs with a circulating anticoagulant represent a difficult problem for treatment, for they will not respond to any substance injected or transfused that might aid the clotting mechanism. As fast as such a substance is transfused, it is deactivated by the circulating anticoagulant.

Some investigators have reported finding enzymes in the blood which may play a key role in the clotting mechanism. One of these enzymes, trypsin, has accelerated clotting in a variety of tests. Although several of these thrombolytic agents have been shown to possess certain clot-accelerating activities in laboratory studies, they have not proven significant in the treatment of hemophilic patients. This kind of research however, could possibly lead to the establishment of a "thromboplastic enzyme" theory of blood coagulation.

Other investigators are studying the activity of the platelets in blood coagulation, the changes that occur to them during clotting, and the role of the thromboplastin factor in platelets which is so essential to normal blood coagulation.

Conclusion.—The National Heart Institute—as of November 1962—was spending more than \$4 million in support of 128 grantee projects with major research emphasis on blood coagulation. Many of these grantees are dealing directly with the problems of hemophilia and related hemorrhagic disorders. Part of the Institute's intramural research, though not specifically concerned with hemophilia, is directed toward obtaining a fuller understanding of the basic biochemical processes governing the mechanism of coagulation.

There is still much to be learned. Scientists so far have been unsuccessful in isolating the antihemophilic factor and defining its molecular structure. One key to future progress may lie in the expansion of protein chemistry studies, not only because of their direct connection with blood studies, but also because of their important link to the study of genetics.

Better ways of treating hemophilia must be found. More and improved concentrates of antihemophilic plasma must be made available at a reasonable price at treatment centers throughout the country. Finally, more time must be spent in helping the hemophiliac and his family adjust to the disease and the forced sedentary life that accompanies it.

DEATHS, DISABILITIES AND COST OF HEART DISEASE

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the National Heart Institute, and the estimated annual cost to the Nation

I. DEATHS FROM CARDIOVASCULAR DISEASES DURING 1961

[National Office of Vital Statistics based on 10 percent sample]

Category	Number
Arteriosclerotic heart disease (includes coronary disease or "heart attacks")	502,351
Cerebrovascular lesions (includes strokes and other blood diseases in the brain)	192,951
Hypertension	75,467
Nonrheumatic chronic endocarditis and other heart muscle degeneration	54,632
General arteriosclerosis	35,388
Rheumatic fever and rheumatic heart disease	17,872
Other cardiovascular diseases	45,961
Total	924,622

II. DISABILITIES FROM CARDIOVASCULAR DISEASES

[Unpublished data of National Health Survey for the period July 1959 to June 1961]

	Disability category		
	Restricted activity	Sick in bed	Away from work ¹
Number of person-days of disability per year (in millions):			
All cardiovascular diseases	454	169	38
Heart conditions	209	82	17
High blood pressure	83	27	6.4
Average number of persons (in thousands):			
All cardiovascular diseases	² 1,244	² 463	³ 158
Heart conditions	573	225	71
High blood pressure ⁴	227	74	27

¹ For those currently employed.

² Person-days/365.

³ Person-days/240.

⁴ Without heart conditions.

III. ESTIMATED ANNUAL COST TO THE NATION

[July 1962 Survey of Current Business, Department of Commerce, unpublished data from Veterans' Administration and National Health Survey]

Compensation and pension payments to veterans disabled by diseases of the circulatory system totaled approximately \$556 million in 1962. Lost productivity for 1961 of those still in the labor force (at estimated \$4,800 average annual earnings) is estimated at \$758 million. Figures on expenses of hospitalization and other medical care are not available, nor are figures on which to estimate the productivity loss of persons no longer in the labor force (retired for disability).

HIGHLIGHTS OF PROGRESS IN RESEARCH ON HEART DISEASE 1962

Items of Interest on Research Studies

Conducted and Supported by the National Heart Institute

ATHEROSCLEROSIS AND CORONARY HEART DISEASE

FIND EXPERIMENTAL EVIDENCE THAT CHOLESTEROL PRECURSOR CAN CONTRIBUTE TO ATHEROMA

Drs. Joel Avigan and Daniel Steinberg of the NHI Metabolism Section report in the "Lancet" (1: 572, Mar. 17, 1962) a rabbit experiment in which desmosterol present in the serum during atheroma formation was found to deposit in the atheroma. The percentage of desmosterol in total atheroma sterols was similar to that in the serum. No experimental evidence had previously been published that desmosterol contributes to atherogenesis.

In the rabbit experiment, an atherogenic diet was fed for 112 days which contained an equal proportion of desmosterol and cholesterol (0.05 percent), plus enough Triparanol (0.1 percent) to block reduction of the desmosterol to cholesterol. This brought enough serum desmosterol into existence (37 percent of all circulating sterols) so that its deposition in the atheroma could be compared with that of the serum cholesterol.

Desmosterol is cholesterol precursor normally absent from the serum. However, desmosterol is usually present in significant quantities in the serum of patients receiving Triparanol (MER-29), a drug that lowers serum cholesterol levels by inhibiting its formation from desmosterol.

In Triparanol-treated patients, the decline in serum cholesterol is usually accompanied by a rise in serum desmosterol. In patients receiving 250 mg. of Triparanol daily, desmosterol may account for about one-fourth of their total serum sterols.

Avigan and Steinberg suggest that total serum sterol levels be used instead of serum cholesterol only, as a measure of the antiatherogenic effects of Triparanol—at least until the atherogenicity of desmosterol can be determined quantitatively in further experiments.

Although Triparanol has been withdrawn from general drug commerce pending further study of its effects in animals, its peculiar ability to alter pathways of sterol biosynthesis assures its continued use in research, both for information on the biology of sterol metabolism and for medically useful clues to the causes of atherosclerosis.

HYPERLIPEMIC AGENT AFFECTS LIPID MOBILIZATION-STORAGE CYCLE, NHI GRANTEE'S OPINE

When the detergent Triton WR-1339 is administered to animals they soon develop hyperlipemia and die within a few months. Prolonged Triton administration causes (1) great accumulation of lipids in the aorta and coronary arteries, (2) marked lipid engulfment by the reticuloendothelial cells of liver, spleen, and lymph nodes, and (3) diffuse depletion of fat stores.

Two NHI grantees recently published their hypothesis about the mechanism of action of Triton based on in vivo experiments in the dog. Drs. Angelo Scanu and Irvine H. Page from the Cleveland Clinic Foundation reported their work in the Journal of Clinical Investigation (41: 495-504, March 1962).

Previous studies, in vitro, showed that Triton combines with the lipid part of lipoproteins, therefore weakening the association between protein and lipid. In vivo experiments using radioisotopes helped to pinpoint further the effects of Triton.

Triton apparently affects the normal fat mobilization and storage cycle—fatty acids are carried to the liver in the form of free fatty acids bound mostly to albumin; they are transported from the liver to fat depots and other peripheral tissues as triglycerides bound to low density betalipoproteins.

Triton acts on the lipoprotein lipids, modifying them so much that they are treated as foreign bodies and removed by the reticuloendothelial system. This action deprives the parenchymal cells of the adipose tissue and of the liver of necessary lipid uptake, thereby stimulating the adipose tissue to release more free fatty acids and the liver to produce more lipoproteins.

PHOSPHOLIPIDS AFFECT BLOOD CLOTTING TENDENCY IN HEART DISEASE, HYPERLIPEMIA

The crippling and lethal effects of atherosclerosis usually result from the blockade of vital blood channels by clots or emboli rather than by the atherosclerotic lesions themselves. The lesion provides a rough calcified surface conducive to clot formation. Further, the high blood lipid levels often associated with atherosclerosis appear to increase the clotting tendency of the blood and to impede its clot-dissolving mechanisms.

One of the factors contributing to the enhanced coagulability often found in atherosclerosis or hyperlipemia may be elevated plasma levels of phosphatidyl ethanolamine and phosphatidyl serine. These two phospholipids appear able to mimic the action of blood platelets in accelerating clot formation and may even be the active principle of platelets. NHI grantees have found that plasma levels of these two phospholipids are two to three times higher in patients with coronary heart disease or hyperlipemia than in normal subjects. The two compounds also comprised a higher percentage of the total plasma phospholipids in the patients.

These findings are reported in *Journal of the American Medical Association* (179: 40-43, Jan. 6, 1962) by Dr. Martin M. Nothman, of the Pratt Clinic-New England Medical Center, Boston, and by Dr. Samuel Proger, of the Tufts University School of Medicine.

LOW BLOOD PRESSURE FOLLOWING CORONARY OCCLUSION DUE TO TWO MECHANISMS

In human coronary occlusion, the early fall in arterial pressure too often proceeds to general circulatory congestion and death in the acute stage of the heart attack. In such cases it may be useful to know if this is due solely to failure of the pumping muscle of the heart or also to inhibition of the nervous instructions to those portions of the blood vessels which help to maintain arterial pressure.

Coronary occlusion was found to cause hypotension indirectly by imbalancing autonomic nervous tone, as well as by direct injury to the heart muscle, according to animal experiments conducted by Dr. LeRoy L. Costantin of the NHI's Laboratory of Cardiovascular Physiology. Dr. Costantin presented his findings at the 1962 Federation meeting in Atlantic City.

Recording the resistance to flow in a main leg artery, and the level of activity in the fibers of the sympathetic nerve to the heart, he found that temporary occlusion of either of the coronary branches on the left side of the heart caused an abrupt drop in both the blood vessel resistance and the sympathetic nerve activity. Both responses to coronary occlusion were restored when the interrupted vagal impulses were restored.

The findings indicate that coronary occlusion stimulates vagal receptors in the heart which reflexly inhibit the sympathetic tone that helps to maintain arterial pressure.

NEW METHOD OF CORONARY ARTERIOGRAPHY EMPLOYS ARTIFICIAL PACEMAKER

Despite the improved quality of coronary arteriograms obtained during acetylcholine-induced cardiac arrest, occasional difficulty in subsequently restoring effective heart rhythm with atropine has prevented widespread clinical application of the combined techniques.

Now, results of animal and clinical studies conducted by Drs. Aydin M. Bilgutay, and C. Walton Lillehei, of the University of Minnesota Medical Center and the Variety Club Heart Hospital in Minneapolis, indicate that this problem has been solved by using an artificial pacemaker to restore normal heart rhythm.

The NHI grant-aided studies were reported in the *Journal of the American Medical Association* (180:1095-1099, June 30, 1962).

As used in coronary arteriography by Drs. Bilgutay and Lillehei, the artificial pacemaker is connected to the heart by an electrically conductive catheter which is passed through the femoral vein and into the right ventricle. Another catheter is passed through the femoral artery to the base of the aorta where the coronary arteries originate.

With both catheters in place, acetylcholine is injected through the arterial catheter to arrest the heart. When the heart ceases to beat, radiopaque contrast substance is injected through the same catheter and X-ray films are exposed. Then the pacemaker is turned on to "restart" the heart. Atropine is preferably not used to counteract the effects of acetylcholine because it is not necessary, and its use occasionally causes abnormalities of heart rhythm including excessively rapid heart beat.

Extensive experimentation with this technique in dogs that had received up to 20 mg./kg. of acetylcholine revealed that heart muscle remained responsive to direct stimulation and artificial pacing, and that normal heart rhythm was quickly restored in these animals. In contrast, 20 mg./kg. of acetylcholine killed all five control dogs that had received only atropine as a countermeasure.

The new method had been used successively in five patients at the time of the Minnesota scientist's report.

SPECIAL CATHETERS PERMIT SEPARATE X-RAY STUDIES ON EACH CORONARY

NHI grantees at the Stanford University School of Medicine have developed a simple, reliable method of selective coronary cine arteriography in animals and man. The new method makes possible the precise localization of injected radiopaque contrast materials in either coronary artery, without the need for an open surgical field.

In most methods of coronary arteriography, radiopaque contrast material is injected through a catheter into the base of the aorta, where the coronary arteries originate. In this way sufficient contrast material enters the coronaries to render them opaque, but contrast material remaining in the aorta often obscures coronary detail. Until recently, most available methods of accomplishing direct coronary injection required either open-chest surgery or surgical exposure of a major artery before catheters could be accurately guided into place with their tips resting in the coronary openings.

These disadvantages have been eliminated by a new method of selective coronary arteriography reported by Drs. H. J. Ricketts and H. L. Abrams in the *Journal of the American Medical Association* (181:620-624, August 18, 1962). Their method uses two preshaped flexible catheters, one for each coronary. Each polyethylene catheter is curved to conform to the aortic arch, with the catheter-tip shaped so as to point toward either the right or left coronary opening.

After piercing the skin and femoral (leg) artery with a hollow needle, one of the coronary catheters, containing a thin guide wire, is inserted into the needle and pushed "upstream" under fluoroscopic guidance into the aortic arch. Then the guide wire is withdrawn, allowing the catheter tip to assume its curved shape. Finally the catheter is advanced into the ascending aorta and manipulated until its tip enters the appropriate coronary opening. Exposure of X-ray film commences with the injection of contrast material (which is followed by immediate withdrawal of the catheter) and continues at a rate of 48 frames per second for a total of 7 to 10 seconds. Thus total cannulation time is less than 20 seconds.

This method of cine arteriography clearly demonstrated the fine peripheral and main coronary branches as well as the coronary veins and coronary sinus in dogs and clinical subjects, the scientists reported. They add, "Since each major artery is studied separately, there is no problem of overlap by the opacified aortic root such as is encountered with nonselective techniques."

HIGH BLOOD PRESSURE

CERTAIN PRENATAL INFLUENCES INDUCE HYPERTENSION IN RATS

A study in animals showing that certain prenatal influences can lead to hypertension and possibly other disorders in the offspring has been reported in the *Journal of Clinical Investigation* (41:710-714, April 1962) by Drs.

Arthur Grollman and Evelyn F. Grollman, NHI grantees at the University of Texas Southwestern Medical School, Dallas.

The offspring in this study are normotensive at birth, but their blood pressure rises slowly and relentlessly until it reaches hypertensive levels at maturity. At autopsy, the animals show no evidence of severe kidney damage, but frequently show enlargement of the left ventricle and moderate thickening of the arterioles.

The diets found to induce hypertension contained excess salt or were deficient in potassium or choline. The hormones were aldosterone, cortisone, desoxycorticosterone, and progesterone. Chlorothiazide, a widely used diuretic, induced hypertension when used alone; but its effects were intensified when it was used in combination with a high salt intake.

When initiated very early in pregnancy, these measures produced severer hypertension in the offspring. However, none produced hypertension if discontinued halfway through pregnancy. Thus their effects appeared to be most pronounced during that stage of fetal development when organ formation was occurring.

Previous studies of this sort have been concerned primarily with structural congenital defects induced by drugs, hormones, or environmental manipulations during pregnancy. This study shows that such prenatal influences can lead to hypertension and possibly other disorders.

The authors feel that these measures probably produce hypertension through some action on the fetal kidneys during early stages of their development. The mechanism may be potassium depletion, especially in the case of chlorothiazide or low potassium diets. This mechanism may also figure in the effects of the various hormones (except progesterone), since they tend to conserve body sodium at the expense of potassium.

EFFECT OF RESERPINE NOT DUE TO NOREPINEPHRINE DEPLETION

NHI scientists show that the effects of reserpine, a widely used tranquilizer and antihypertensive drug, are not due to its depletion of norepinephrine (NE) storage sites.

Reserpine is widely used as a tranquilizer and to lower high blood pressure. It is known to affect storage sites in the brain for serotonin (5HT) and norepinephrine (NE), but the mechanisms by which reserpine causes behavioral and neurologic changes are not known.

Drs. G. L. Gessa, E. Costa, R. Knutzman, and B. B. Brodie, of the NHI Laboratory of Chemical Pharmacology, used alpha-methyl metatrosine (MMT), an amino acid which selectively depletes brain NE to study reserpine action. Their findings are reported in *Life Sciences* (8), 353-360, August 1962.

They compared the effect of MMT with that of reserpine on behavioral changes, electrophysiologic phenomena and the concentrations of 5HT and NE in various areas of the brain.

Reserpine depleted the 5HT and NE in the brain, produced hyperactivity followed by a depressed period and characteristic changes in evoked potential of the limbic system of the brain. This part of the central nervous system seems to be involved in learning, and in the regulation of emotional behavior. When MMT was administered, NE in the brain was depleted, but MMT produced none of the behavioral or electrophysiologic changes produced by reserpine. Pretreatment with MMT in order to deplete NE did not diminish the neurologic effects of reserpine, furnishing evidence that a factor other than depletion of NE in the brain is responsible for these reactions. Depletion of 5HT correlated with response to reserpine and suggests a possible relationship between the two. However, further studies are needed to clarify the role of 5HT.

DEVELOP MORE SENSITIVE METHOD FOR MEASURING MONOAMINE OXIDASE

National Heart Institute scientists describe a sensitive method for measuring monoamine oxidase (MAO) *in vitro* in organs with low levels of enzyme activity, thereby facilitating study of MAO inhibitors, used as antihypertensive drugs, in these tissues.

Usual methods for determining activity of the monoamine oxidase (MAO) enzyme system in various tissues involved either measurement of substrate disappearance (that is, how much of a particular amine disappears, apparently metabolized by MAO) or measurement of oxygen uptake. However, these methods are not adequately sensitive for use in tissues with low enzyme activity, such as dog heart or a single sympathetic ganglion. And yet, in order to study

the action of MAO inhibitors on these tissues, it is important to be able to assay enzyme activity. MAO inhibitors are widely used to lower blood pressure.

Investigators at the National Heart Institute found that tryptamine, a good substrate for MAO, can be recovered as indoleacetic acid (IAA) if aldehyde dehydrogenase (AD) and DPN are added to the preparation. The fluorescent properties of IAA make it easily detectable even in microgram quantities.

This method has already permitted demonstration that marked inhibition of MAO in the sympathetic ganglia of dogs and cats occurs within a few minutes after injection of a potent MAO inhibitor. This sensitive assay can be applied to studies of MAO activity in specific parts of the central and peripheral nervous system, to studies of the action of cardiovascular drugs on MAO in the heart, and to studies clarifying relationships between pharmacologic and biochemical effects of MAO inhibitors.

The method, developed by Walter Lovenberg, Dr. Robert J. Levine, and Dr. Albert Sjoerdsma of the Heart Institute's Experimental Therapeutics Branch, was reported in the *Journal of Pharmacology and Experimental Therapeutics* (135: 7-10, January 1962).

STUDIES MAY EXPLAIN WHY CERTAIN MAO INHIBITORS LOWER BLOOD PRESSURE

Studies by NHI scientists indicate that certain MAO inhibitors may lower blood pressure by blocking the release of norepinephrine (NE) at sympathetic nerve terminals. Since NE is the chemical messenger between these terminals and their target organs, such a blockade would effectively prevent sympathetic nerve impulses calling for blood vessel constriction from reaching the muscles of the blood vessel wall.

These findings, by Drs. G. L. Gessa, Edwardo Cuenca, and Erminio Costa, of the Laboratory of Chemical Pharmacology, were presented at the fall pharmacology meeting held in Nashville.

The scientists tested a number of MAO inhibitors against norepinephrine release induced by guanethidine. This antihypertensive drug closely mimics the norepinephrine-releasing action of the nerve impulse. Thus this system provided a model for testing whether the MAO inhibitors would prevent the release of norepinephrine by sympathetic nerve impulses.

All of the MAO inhibitors tested were hypotensive agents. In varying degrees, all of these drugs inhibited the release of norepinephrine by guanethidine. This finding suggests that these drugs may also prevent sympathetic nerve impulses from releasing norepinephrine, and may thus reduce blood pressure by halting vasoconstrictive messages short of their targets.

The MAO inhibitors are so named because they block the action of an enzyme largely responsible for inactivating norepinephrine, epinephrine and other biologically active amines. The present studies provide a plausible explanation for the blood-pressure effects of these drugs, but revealed no correlation between their potency as MAO inhibitors and their potency in blocking NE release by guanethidine. The two actions may be unrelated, and MAO inhibition per se may play no role in the blood pressure effects of these drugs.

NEW DRUG FOUND INEFFECTIVE AGAINST HYPERTENSION IN GRANTEE STUDIES

Mebutamate (Capla, Wallace), a derivative of the tranquilizer Miltown (Wallace), has been reported to be an antihypertensive agent. However, NHI grantees report that the drug was ineffective when tested against mild to moderate hypertension in 19 geriatric patients.

Drs. G. A. Porter, M. D. Baird, and H. E. Griswold, of the University of Oregon, assessed the clinical effectiveness of mebutamate by means of a double-blind random crossover method. Each patient received either mebutamate or an indistinguishable placebo for a certain period, then was switched from one to the other. Neither the doctor nor the patient knew which the patient was receiving or when the switch was made. The drug was considered clinically effective if it lowered diastolic blood pressure by 10mm/Hg or more.

The scientists observed no significant antihypertensive effect in any of the patients throughout the 4 months of the study.

Their findings are reported in the *American Heart Journal* (63: 754-756, June 1962).

CERTAIN ENZYME INHIBITORS BLOCK NOREPINEPHRINE, EPINEPHRINE SYNTHESIS

Dopamine-beta-oxidase is the enzyme that catalyzes the conversions of dopamine to norepinephrine and epinephrine. Several compounds that inhibit this enzyme effectively block the production of norepinephrine and epinephrine *in vivo*, but do not interfere with the production of serotonin and other biologically important amines derived from dopamine.

Blocking the synthesis of these two catecholamines has great potential medical interest because of the role they are suspected of playing in essential hypertension. This new family of enzyme inhibitors—the first agents found thus far that effectively block the synthesis of these amines in the body—may therefore be valuable research tools.

These inhibitors have about the same molecular size and shape as dopamine—the substance ordinarily processed by dopamine-beta-oxidase—but differ from dopamine in chemical structure. Nevertheless, the similarities are strong enough to fool the enzyme into taking on one of these foreign compounds. Having done so, the enzyme can neither convert that compound to norepinephrine nor easily get rid of it. The enzyme is thus effectively put out of action. Eventually, so many enzymes are tied up that norepinephrine production in the tissues is sharply curtailed.

Although certain of the dopamine-beta-oxidase inhibitors have been shown to block norepinephrine and epinephrine production in laboratory animals, the physiological consequences of that blockade remain to be evaluated. Preliminary studies also indicate that the present crop of inhibitors are far too toxic to warrant serious consideration as potential therapeutic agents.

The NHI studies were done by Drs. Carolynne Hirsch, Ronald Kuntzman, Erminio Costa, and Bernard B. Brodie, of the laboratory of chemical pharmacology; and by Drs. B. Nikodijevic, C. R. Creveling, and Sidney Udenfriend, of the laboratory of clinical biochemistry. Their findings were reported in *Life Sciences* (3), 85-92, March 1962.

The dopamine-beta-oxidase inhibitors used in the studies were synthesized and supplied to NHI by Mr. E. M. Bavin, of Smith & Nephew, Ltd., England, and by the Warner-Lambert Research Institute, Morris Plains, N.J.

SURGERY

TECHNIQUE MINIMIZES HAZARD OF CALCIFIC EMBOLI AFTER REPAIR OF AORTIC VALVE

In acquired diseases of the aortic valve, the valve leaflets and surrounding tissues are often densely calcified. Corrective surgery usually involves removing the calcific and fibrous material from the leaflets (debridement) or replacing them, partially or completely, with prosthetic devices. In either procedure it is essential that all calcific debris be removed from the heart. Otherwise this debris may form emboli that can plug essential blood vessels and cause serious disability or death.

This hazard is minimized by a technique reported in *Surgery, Gynecology and Obstetrics* (114: 634-635, May 1962) by Drs. Andrew G. Morrow and W. Gerald Austen, of the NHI surgery branch.

Before initiating heart-lung bypass, the scientists pass a cannula to the tip of the left ventricle. During the operation, the aspirated blood is returned to the heart-lung machine, first passing through a bubble-filter trap that removes any debris. When the aortic valve repair is completed, the flow from the cannula is diverted into the waste vessel. The aorta and left ventricle are then irrigated with several liters of saline while suction on the cannula is increased. After all saline and debris have been removed, the flow is diverted back to the heart-lung machine.

The scientists have used this technique successfully in 54 operations. After every procedure, calcific and fibrous particles in varying sizes and numbers turned up in the waste vessel; but none turned up as emboli in any of the patients.

WHOLE BODY PERFUSION IS SIMPLIFIED BY USE OF PLASMA EXPANDER

Drs. Richard A. DeWall and C. Walton Lillehei, of the University of Minnesota Medical School, report in the journal of the American Medical Association (179: 430-434, February 10, 1962) their experience with a simplified technique of whole body perfusion during open-heart operations. Dr. Lillehei is a grantee of the Heart Institute.

The surgeons used low molecular weight dextran, a plasma expander that also prevents blood cell clumping during perfusion, to replace a large proportion of the blood normally used to prime the heart-lung machine. The method thus eliminates the necessity of procuring large quantities of blood as a prerequisite to scheduling open-heart operations. The use of moderate hypothermia and reduced perfusion rates contributed to the simplicity and safety of the technique.

Experience with 27 consecutive patients have borne out the advantages of this method. Besides the smaller quantity of blood required, the method reduces the likelihood of transfusion complications and induced metabolic acidosis. Perfusions for periods longer than 2 hours are also much safer with this method, the scientists report.

PLASTIC ADHESIVE THAT BONDS TISSUE MAY PROVE USEFUL IN SURGERY ON HEART, VESSELS

A new plastic adhesive that bonds firmly to many tissues may prove useful for controlling bleeding during surgery on the heart and great vessels. The compound, called Eastman 910 Monomer, polymerizes swiftly under pressure in the presence of moisture to form an adhesive that bonds firmly to many tissues.

Drs. Nina Braunwald and William Awe, of the NHI surgery branch, have tested this adhesive in animal experiments to determine whether it might serve in lieu of sutures to stop bleeding from the heart and great vessels, to repair septal defects, or to secure artificial heart valves.

They report in *Surgery* (51: 786-792, June 1962) that the adhesive served extremely well in sealing holes in the aorta with muscle patches taken from the chest wall. These seals withstood blood pressures of 300 to 400 millimeter hectograms without rupturing, and stopped bleeding with equal effectiveness in heparinized and nonheparinized animals. It also performed well in repairing holes in the heart itself when the muscle patches were applied to the outer surface.

Patches of porous synthetic materials were less successful than muscle patches because the adhesive effectively sealed the pores and prevented the ingrowth of host tissue necessary for firm healing. It was also generally unsuccessful in repairing septal defects and in securing artificial valves because it did not adhere well enough to the inner surfaces of the heart.

The authors conclude that although the adhesive is unlikely to supplant sutures in cardiovascular surgery it may replace sutures in situations where weakened blood vessel walls or coagulation defects exist.

VEIN PATCH-GRAFT BEST FOR REPAIRING BLOCKED FEMORAL ARTERY IN MAN

A NHI grant-aided study indicates that reconstruction of the superficial femoral artery, following the surgical removal (endarterectomy) of atherosclerotic deposits from this small leg artery, is best accomplished by the use of a long patch-graft autogenous vein.

The small size of the superficial femoral artery and its location in an area subjected to continual mechanical stress, are conducive to thrombosis and reocclusion of the artery following endarterectomy. This reocclusion can be prevented by using a trip of saphenous vein, taken from the patient's leg, to widen the femoral artery during its reconstruction, according to findings reported in *Surgery* (51: 58-61, January 1962) by Dr. W. Sterling Edwards, from the Medical College of Alabama, Birmingham.

Dr. Edwards employed the vein-patch method in a consecutive series of 20 femoral artery reconstructions and followed the patients for from 9 to 18 months postoperatively. Arteriograms revealed that 18 of the 20 arteries remained widely patent: both failures were due to infection in the incision, he reports. There was no evidence of aneurysmal dilation—the ballooning of thin-walled venous grafts when subjected to the higher prevailing pressures of the arterial circulation, especially when replacing portions of larger arteries.

The successful results obtained in this study indicate that wider use should be made of endarterectomy in patients with superficial femoral artery occlusion. Formerly resorted to only when symptoms were very severe—impending gangrene or severe pain in the resting limb—endarterectomy may now be advisable in patients suffering only from calf pain during exercise, especially if walking is an economic necessity to these patients.

ALKALOSIS PROTECTS THE HEART BETTER THAN ACIDOSIS DURING PROFOUND HYPOTHERMIA

Findings from NHI surgical experiments indicate that alkalosis protects the heart better than acidosis during profound hypothermia. Since profound hypothermia limits the ability of hemoglobin to yield the oxygen it carries to the tissues, some scientists have advocated increasing blood acidity to facilitate the process. Better spontaneous recovery of heartbeat has been reported when dilute hydrochloric acid was used to lower the blood pH during profound hypothermia.

Alkalosis during profound hypothermia (50 to 60° F.) protected the ability of the heart to resume work after 30 minutes of anoxic arrest. Acidosis, on the other hand, resulted in severe depression of ventricular function, following recovery from profound hypothermia. When blood flow is maintained at a high rate during profound hypothermia, the induction of acidosis would appear to serve no useful purpose in surgery.

These are findings from dog experiments by Drs. Paul A. Ebert, Lazar J. Greenfield, W. Gerald Austen, and Andrew G. Morrow of the NHI clinic of surgery.

The NHI scientists found that induced acidosis did not significantly increase total oxygen consumption in dogs during profound hypothermia. They suggest that the reduced metabolic demands of tissues cooled to 50° may not require activation of the hemoglobin system when high flow rates are maintained by the heart-lung machine.

Further, destructive protein-digesting enzymes can be activated by increased acidity. The cellular damage which occurs in the anoxic heart has been shown to be related to the low pH which results from anoxia. Alkalosis might tend to protect against this.

The NHI report appears in *Surgery, Gynecology and Obstetrics* (114: 357-362, March 1962).

DIRECT SURGICAL APPROACH USED BY NHI GRANTEES TO REPAIR ANEURYSMS

Drs. Charles A. Hufnagel and Peter W. Conrad of the Georgetown Medical Center recently reported in *Surgery* (51: 84-89, January 1962) their direct approach to repair of dissecting aneurysms of the ascending aorta. The NHI grantees used cardiac cooling to maintain cardiac arrest during surgery.

Although dissecting aneurysms, in which blood is forced between the inner and outer walls of an artery, were once considered sudden and usually fatal, more and more experience has shown that in the majority of cases, there is ample time for diagnosis and treatment. Techniques such as contrast angiography make possible accurate diagnosis and evaluation.

Drs. Hufnagel and Conrad used a direct approach to repair aneurysms in the ascending aortas of seven patients. They cooled the heart to below 10° C. while maintaining the body temperature at 30° C. Cardiac cooling can be safely used to maintain cardiac arrest without coronary perfusion for 20 to 120 minutes even in patients with diseased hearts. They repair the aortic defect by sutures and sometimes by excising the damaged portion and replacing it with a prosthesis.

Five of the seven patients have survived and remain well for periods of between 6 and 18 months.

PERIPHERAL RECEPTORS PLAY MAJOR ROLE IN CARDIAC ARREST DUE TO HYPOXIA

Cardiac arrest during hypoxia results primarily from stimuli originating in the peripheral nerve receptors rather than from direct effects of oxygen deficit on the heart. These studies were reported at the October meeting of the American College of Surgeons, Atlantic City, by Drs. Paul A. Ebert, Lazar J. Greenfield, and W. Gerald Austen, of the NHI cardiology branch.

The investigators used two heart-lung machines, so that the coronary circulations and the systemic circulations could be perfused independently. When the heart was perfused with blood low in oxygen but the systemic circulation was perfused with fully oxygenated blood, no significant change in heart rate or rhythm was noted.

However, when hypoxia was produced in the systemic circulation, heartbeat slowed abnormally in all animals and ceased altogether in two of them, even though their hearts were being perfused with fully oxygenated blood.

Sudden systemic hypoxia produced more severe reactions than gradual hypoxia. The most severe reactions occurred when both the systemic circulation and the cardiac circulation were perfused with blood low in oxygen.

When the vagal nerves leading to the heart were severed, the effects of systemic hypoxia were abolished.

The investigators concluded that decreased levels of oxygen in the systemic circulation somehow stimulate neural receptors which can slow and even stop the heart. This can happen even when the heart itself is receiving adequate oxygen from its own blood supply.

NEW KNOWLEDGE AND METHODS

ENERGY UTILIZATION IMPAIRED IN THE FAILING HEART, NHI GRANTEES REPORT

In congestive heart failure, the heart is unable to make full use of its available stores of adenosine triphosphate (ATP), the high-energy fuel that powers heart muscle contraction, according to findings reported in the *American Journal of Physiology* (202: 940-946, May 1962) by Drs. Norman R. Alpert and Michael S. Gordon, NHI grantees at the University of Illinois College of Medicine, Chicago. This impairment, probably an important factor in the inadequate power output of the failing heart, appears to stem from alterations in the contractile protein of heart muscle, they report.

ATP is the immediate source of power for virtually all of the body's energy-consuming processes. Energy generated by the combustion of food is stored as readily available chemical energy in the phosphate bonds of this compound. When needed, this energy is tapped by enzymes called ATPases. These split the phosphate bonds of ATP and harness the liberated energy to perform useful works.

The ATPases activity of heart muscle thus provides a reliable index of its ability to do work.

Drs. Alpert and Gordon compared ATPase activity in heart muscle tissue obtained at autopsy from normal hearts with ATPase activity in similar tissue from patients who had died of congestive heart failure. Both groups of samples were incubated under biochemical conditions favoring maximum ATPase activity. The comparison revealed that ATPase activity in the samples from heart failure victims averaged 35 percent lower than that in the normal tissue samples.

The contraction of heart muscle apparently involves the interaction of two contractile proteins; myosin and actin. Myosin appears to be the ATPase that makes the energy of ATP available to drive the contractile mechanism. Thus, the scientists point out, the mechanism underlying decreased ATPase activity in congestive heart failure probably stems from structural alterations in either or both of these proteins.

Even under normal conditions, such an impairment of energy utilization might hamper the efforts of the heart to meet its circulatory obligations. In the development of congestive heart failure, circulatory conditions could hardly be called normal.

Usually, the heart is taxed relentlessly with a heavy, steadily increasing circulatory load. When the heart enlarges—as it usually does in an attempt to meet these exorbitant demands—it eventually reaches a point beyond which its mechanical pumping efficiency begins to dwindle. As a result, it must expend more and more energy merely to accomplish the same amount of work.

Under circumstances such as these, the diminished capacity for generating and using energy could well prove disastrous.

NEUROPHYSIOLOGIC FUNCTION IN NEWBORN MAMMALS DETERMINED BY BRAIN AMINE LEVELS

The guinea pig is born with a highly developed central nervous system, and displays well-defined behavior patterns that enable him to fend for himself almost from the moment of birth. In contrast, the rabbit and rat are almost completely helpless at birth, and develop well-defined behavior patterns only after several weeks of postnatal life. NHI studies suggest that the wide differences in neurophysiological function between the newborn of these species may be related to the capacity of their brains to synthesize and store norepinephrine and serotonin, amines which have been implicated in the coordination of primitive behavior patterns.

These studies were conducted by Dr. N. Karki, of the University of Helsinki, Finland, and by Drs. Ronald Kuntzman and Bernard B. Brodie, of the NHI Laboratory of Chemical Pharmacology. Their findings were reported in the *Journal of Neurochemistry* (9: 53-58, January 1962).

They found that, whereas brain norepinephrine and serotonin levels in the newborn guinea pig were the same as those of the adult, these levels were much lower in the newborn rabbit or rat. In the rat, brain serotonin reached adult levels only after 3 weeks of life, and brain norepinephrine was still somewhat below adult levels after 6 weeks.

The low brain amine levels in newborn rabbits appeared to result primarily from a limited capacity to store them. The scientists opine that amine synthesis and amine storage are probably closely linked processes but that the rate of amine synthesis is less important in determining brain amine levels than is the number of available storage sites and their capacity. This is because amines that cannot be stored are rapidly destroyed by enzymes.

Both norepinephrine and serotonin appear to be stored at or adjacent to nerve junctions. As the brain matures and additional neuronal pathways develop, the number of available storage sites increases. As a result, brain amine levels rise.

The scientists observed that the development of the various components affecting the synthesis, storage, and metabolism of norepinephrine and serotonin correspond closely with the development of neurophysiological function in the rabbit and rat. Thus these biochemical processes may be important facets of a single event: the maturation of nervous conduction in the central nervous system.

CAROTID SINUS BARORECEPTORS RESET IN ENDOTOXIN SHOCK

Studies by NHI grantees indicate that, in endotoxin shock, the pressure sensitivity of baroreceptors in the carotid sinus may be reset to stabilize blood pressure at hypotensive levels. This finding is reported in the *American Journal of Physiology* (202: 971-977, May 1962) by Drs. John W. Trank and Maurice B. Visscher of the University of Minnesota.

The carotid sinus is a specialized receptor that reacts to changes in carotid artery pressure by initiating reflexes to compensate for those changes. When carotid artery pressure is high, the sinus increases the activity over its afferent nerve fibers to the central nervous system. The central nervous system responds with measures that reduce central systemic pressure; decreased heart rate and output and decreased peripheral resistance. Conversely, carotid artery hypotension decreases the carotid sinus input into the central nervous system and leads to the initiation of measures to increase central systemic pressure; increased heart rate and output and increased peripheral resistance.

Drs. Trank and Visscher studied the activity of the carotid sinus in endotoxin shock, using animal preparations that enabled them to perfuse the carotid sinus at a constant pressure. They recorded activity in the carotid sinus nerve before and after inducing shock with *E. coli* endotoxin.

For any given carotid sinus perfusion pressure, the scientists found that the endotoxin increased the carotid sinus discharge along its afferent fibers. In effect, the endotoxin had reset the barostatic mechanism to stabilize blood pressure at hypotensive rather than at normotensive levels. This alteration in the barostatic setting was observed to persist for as long as 2 hours after administration of the endotoxin.

The scientists feel that this barostatic resetting may play a dominant role in maintaining hypotension in the later phases of endotoxin shock. It may also reduce the capacity of the homeostatic mechanisms to compensate for the profound hypotension initially produced by administration of endotoxin.

The mechanism by which the barostat is reset is not clear. The endotoxin may act directly on the carotid sinus baroreceptors to increase their sensitivity to carotid artery pressure or these effects might be caused by epinephrine, serotonin, histamine, or other substances released into the blood in endotoxin shock.

RESPIRATORY CENTER IN BRAIN MEDIATES BREATHING RESPONSE TO CO₂ INHALATION

Physiologists agree that inhaled carbon dioxide (CO₂) acts as a respiratory stimulant, but disagree as to its site (as well as to its mode) of action. According to most investigators, blood CO₂ is monitored centrally by chemoreceptors in the brain's respiratory center which controls, via efferent nerve pathways to

the respiratory muscles and lungs, breathing rate and volume. Some scientists, however, claim that CO_2 is detected peripherally by chemoreceptive areas of the carotid artery and aorta, as well as centrally. Still others, noting the increased concentration of venous CO_2 during muscular exercise, postulate the existence of other chemoreceptors in the great veins and/or lungs that have an additional influence on respiration during exercise.

The majority opinion, that CO_2 -sensitive chemoreceptors in the brain, rather than elsewhere in the body, mediate the increased breathing rate and volume resulting from CO_2 inhalation, is substantiated by cross-circulation experiments conducted by Drs. F. F. Kao, R. G. Suntay, and W. K. Li, of the State University of New York, Downstate Medical Center, in Brooklyn, N.Y. In each of nine experiments, they joined the circulatory systems of two dogs in such a way that one dog (the donor dog) maintained blood circulation in its entire body as well as the head of a recipient dog. After carefully tying off all vascular communications between the recipient's head and body (but leaving nerves and trachea intact), the investigators gave the donor dog CO_2 to breathe, and measured the ventilatory responses of both dogs.

Thus, with the recipient's respiratory center isolated from any possible influence of peripheral chemoreceptors but exposed to experimentally induced variations in donor-blood CO_2 concentrations, respiration in this animal would reflect only the activity of centrally located chemoreceptors; whereas respiratory responses of the donor dog would show the additional influence, if any, of peripheral chemoreceptors.

Comparison of the ventilatory responses showed they were the same in both donor and recipient dogs following CO_2 inhalation by the donor. From this finding, the scientists conclude that peripheral chemoreceptors play no significant role in mediating respiratory sensitivity to CO_2 , but that this function is performed exclusively by the medulla's respiratory center.

These studies were aided by a NHI research grant, and reported in the *American Journal of Physiology* (202: 1024-1028, May 1962).

DEMETHYLATION TRANSFORMS CERTAIN TRANQUILIZERS INTO ANTIDEPRESSANTS

Removing a single methyl ($-\text{CH}_3$) group from trifluopromazine and certain other chlorpromazinlike compounds converts these tranquilizing agents into powerful antidepressants.

These findings, by Drs. Marcel H. Bickel, Fridolin Sulser, and Bernard B. Brodie, of the NHI Laboratory of Chemical Pharmacology, were reported in *Pharmacologist* (4: 159, fall 1962).

The idea for the chemical modification of trifluopromazine and its near relatives arose from earlier studies on the antidepressant drug Imipramine (Tofranil, Geigy). The studies had shown that desmethylimipramine, the metabolite resulting from the demethylation of Imipramine, was responsible for the antidepressant effects attributed to Imipramine. The parent drug proved to be a sedative that actually interfered with the action of its metabolite.

Noting the structural similarities between Imipramine and certain chlorpromazinlike tranquilizers, the scientists reasoned that the demethylation of these compounds might bring about a similar Jekyll-and-Hyde transformation in their actions. This proved to be the case. Several of these modified compounds were able to block the syndrome of central nervous system depression induced in animals by sedative doses of reserpine. In the past, the effectiveness of antidepressants against this syndrome in animals has proved to be a reliable index of their effectiveness against naturally occurring endogenous depression in man.

Since desmethylimipramine has already proved its worth in clinical trials, it appears likely that these new compounds may also find clinical application against certain mental disorders.

ACTIVE TRANSPORT MECHANISM IN RENAL REABSORPTION OF CHLORIDE

Studies by NHI grantees provide strong evidence that, in the latter half of the kidney tubule, chloride is reabsorbed by an active transport mechanism as well as by passive diffusion. These studies are reported in the *Journal of Clinical Investigation* (41: 101-107, January 1962) by Drs. Floyd C. Rector, Jr. and James R. Clapp, of the University of Texas Southwestern Medical Center, Dallas.

Most of the blood that flows through the kidney must pass through the kidney filtration units (glomeruli), where protein-free plasma is removed for processing by the kidney tubules. As the plasma passes through the tubules, most of its

original complement of water, electrolytes, and nutrients is reabsorbed. Some substances are passively reabsorbed; others are reabsorbed through active transport mechanisms that expend metabolic energy to move these substances out of the tubule against unfavorable concentration or electrochemical gradients.

No active transport mechanism has been postulated for chloride reabsorption because it appeared that none was needed. The active transport of large quantities of sodium, which is positively charged, makes the exterior of the tubule electrically positive relative to the interior. This electrical gradient exerts a strong force tending to pull the negatively charged chloride out of the tubule.

The only opposing force is that exerted by the chloride concentration already outside the tubule, which is about the same as that of plasma. In the proximal segment, the chloride concentration inside also approaches that of plasma; so the concentration gradient is too slight to offer much opposition. Further along, however, as the chloride concentration inside continues to fall while the outside remains about the same, the concentration gradient becomes steeper and steeper. Eventually, in the distal segment, the gradient may become steep enough to offset the electrical gradient and to halt further passive reabsorption of chloride.

Drs. Rector and Clapp studied chloride reabsorption in the distal tubule segment in normal and salt-depleted animals. By continuous infusions of sodium sulfate, which favors chloride reabsorption, they were able to produce very steep chloride concentration gradients in this segment.

They compared the calculated forces exerted by the chloride concentration gradients and electrical gradients determined at numerous points along the distal segment. They found that chloride continued to move out of the tubule even when the concentration gradient had become so steep that, theoretically, it could not be overcome by the favorable electrical gradient. They reasoned that the extra energy required to move chloride against this unfavorable gradient must therefore have been provided by an active transport mechanism.

NHI EXPERIMENTS SHOW HEART PERFORMANCE NOT BENEFITED BY DRUG, ANGIOTENSIN II

Drs. Edmund Sonnenblick and S. Evans Downing, of National Heart Institute's Laboratory of Cardiovascular Physiology, report from cat experiments that angiotensin II increases blood pressure but produces no sustained increase in the muscular strength of the heart. The hope that angiotensin might have medically useful cardiotonic effects was raised by earlier reports that single large doses may increase ventricular contractility. However, this was found to be only transitory when Sonnenblick and Downing administered it continuously to cats in solutions strong enough to greatly increase blood pressure.

The effect of angiotensin II on electrical activity in the cardiac sympathetic nerve, which strengthens the heartbeat, was also recorded in the cat experiments of Sonnenblick and Downing. Their electroneurographic tracings from the cats showed that the activity of this nerve was depressed as angiotensin elevated the blood pressure.

Comparing angiotensin II with norepinephrine in cats, it seems that their like effects on blood pressure are accompanied by unlike and possibly opposing effects on heart performance.

This report is published in *Clinical Research* (10: 181, April 1962).

ION EXCHANGE RESINS REVERSE BIOCHEMICAL ALTERATIONS IN STORED BANK BLOOD

Blood stored in acid-citrate-dextrose (ACD) solution, the most widely used anticoagulant and preservative for banked blood, undergoes undesirable biochemical changes that make it unsafe for transfusion in large quantities.

Of major importance are increased acidity and increased concentrations of potassium, citrate, and ammonia in ACD-treated blood. Massive transfusions of this blood may produce (1) elevated serum potassium concentrations, which increase the irritability of heart muscle and may cause cardiac arrest; (2) citrate intoxication, with possible convulsions, impaired clotting, and cardiac arrest; and (3) ammonia intoxication, with stupor and coma.

Drs. J. L. Sandler, T. F. Nealon, Jr., and J. H. Gibbon, Jr., NHI grantees at Jefferson Medical College, Philadelphia, report in the *Journal of the American Medical Association* (179: 201-203, Jan. 20, 1962) that these changes in ACD-treated blood can be reversed and the blood's biochemical normalcy restored by passing it through a column containing a mixture of cation and anion exchange resins.

The cation exchange resin of the column selectively removes excessive positively charged ions (such as potassium and ammonium) from the blood, and the anion exchange resin removes excessive negatively charged ions such as citrate. Two other resins remove enough acid molecules and carbon dioxide to restore normal blood pH (a slightly alkaline 7.4).

Earlier the scientists had processed the ACD-treated blood in two separate columns, one to remove positively charged ions, the other to remove negatively charged ones. This procedure removed most of the excess electrolytes, but led to elevated levels of calcium ion that made the blood tend to clot.

The reason: The anticoagulant of ACD solution is citrate. It works by tying up the calcium ions that are essential to normal blood clotting. The cation column, which would have ordinarily removed the positively charged calcium, could not do so because the calcium was too firmly attached to citrate. However, the anion exchange resin of the second column was able to break this bond, removing the negatively charged citrate and leaving free calcium ions behind.

The scientists solved this problem by incorporating both resins into the same column. The cation resin picked up the calcium ions liberated as citrate was removed by the anion resin.

The "combination of ingredients" column was able to restore nearly normal electrolyte concentrations and pH values to ACD-treated blood, the scientists report.

STUDIES SHOW METHYSERGIDE EFFECTIVE IN PREVENTING MIGRAINE HEADACHE

NHI grant-aided studies indicate that the antiserotonin agent, methysergide (Sansert, Sandoz), is a promising prophylactic drug for the successful management of uncomplicated vascular headache (migraine).

Prophylactic use of methysergide benefited a majority of patients with severe, frequent migraine not associated with tension or other psychogenic components, in studies reported by Drs. Alfred R. Hale and Afrian F. Reed, of the Feazel Laboratory for the Study of Cerebral Circulation and Migraine, Tulane University School of Medicine, and the Charity Hospital of Louisiana in New Orleans.

For this study, Drs. Hale and Reed carefully selected 57 patients whose migraine seizures occurred more frequently than once a week. The patients comprised two groups: those whose headaches were of the uncomplicated type (33 patients); and those whose headaches were of the mixed type associated with a significant tension component, drug dependency, or both (24 patients). Criteria for selection were based on complete medical histories and on diagnostic tests that included a positive therapeutic response to ergotamine tartrate (ergot alkaloids are the principal drugs used in the symptomatic treatment of migraine). Ergotamine tartrate was also used during the testing period as an index of the efficiency of methysergide prophylaxis. Thus, patients who responded to methysergide would not require ergotamine tartrate except during the placebo period.

Following an initial 3-week loading period, when 6 mg. of methysergide daily was given to all patients, dosage was gradually reduced to lower maintenance levels in responsive patients, then either drastically reduced or replaced with placebo medication during control periods.

The investigators found that 69 percent (23) of migraine patients presenting the uncomplicated type of headache responded favorably to methysergide prophylaxis, with either complete remission or notable reduction in severity and frequency of symptoms. Only three of those with mixed headache, however, responded favorably. An additional finding from the study, normalization of the electroencephalogram (which was abnormal in 29 percent of the patients studied) in migrainoid patients who responded successfully to methysergide treatment, "suggests the possible effectiveness of this agent in the management of convulsive disorders," the scientists report. They conclude that although these results with methysergide are encouraging, the drug requires further evaluation.

Their findings, which extend earlier observations elsewhere on the use of methysergide in migrainoid patients, appeared in the *American Journal of the Medical Sciences* (243: 146-152, January 1962).

HISTIDINE DECARBOXYLASE INHIBITION MAY INHIBIT CELL DIVISION IN TUMORS

Several lines of evidence from NIH-aided work in Lund, Sweden, relate activation of histidine decarboxylase to rapid rates of growth, or cell division, in both normally differentiating and malignant forms of mammalian tissue.

Histidine is one of those protein constituents which is essential in the diet for normal tissue growth and repair, at least in youngsters. Adult persons seem

capable of synthesizing enough of this amino acid to sustain themselves, under ordinary conditions. The enzyme, histidine decarboxylase, acts to convert histidine to histamine; so the histamine-forming capacity of a tissue is a good measure of its histidine decarboxylase activity.

The first evidence relating the activity of this enzyme to very high rates of mammalian tissue growth, was reported in 1960 from studies in rat embryos by G. Kahlson's team at the University of Lund, Sweden. The histidine decarboxylase activity was especially striking in the liver, an organ in which the time of highest histamine-forming capacity coincides fairly closely with the time of greatest hemopoietic, or blood-cell forming activity. This indicates a direct link between the activity of this enzyme and the high rate of cell propagation, or mitosis, in the tissue.

Further strengthening this relationship was the finding that artificial elevation of histidine decarboxylase activity accelerates wound healing and increases the content of collagen, a connective tissue protein, in the granular tissue which fills wounds. Conversely, inhibition of this enzyme resulted in slower wound healing and reduced collagen content in the wound scar.

They later found that histidine decarboxylase was activated during the growth of malignant mammary tissue in female rats (Walker rat mammary carcinoma transplants). A similar finding, with a type of liver tumor in rats, was reported in 1960 by another research team.

Current work, reported by the Lund group (Kahlson, Elsa Rosengran, and Claudia Steinhardt) in the *Journal of Physiology* (160: 12-13, February 1962), involved experiments with tumors growing as free single cells in the peritoneal cavity of mice (Landschutz I tumors). The use of this type of tumor enabled accurate counts to be made of the total number of cells in a single tumor, and enabled identification of growth phases in the tumor from the frequency of dividing cells (mitotic figures) at different time intervals after the tumor was implanted in the mouse.

Administration of C^{14} labeled histidine showed that the phases of maximum histidine decarboxylase activity (maximum appearance of labeled histamine) coincide with the phases of maximum growth activity (greatest frequency of cell divisions, or mitotic figures) in the tumors.

The Lund grantees are now engaged in experimental attempts to arrest tumor growth by enzyme inhibition.

UNIQUE ANTICOAGULANT ACTION SHOWN BY MAO INHIBITOR IN NHI GRANTEE STUDIES

NHI grant-aided animal experiments demonstrate the unique action and superiority of nialamide over two orally administered anticoagulants in preventing intravascular blood clot formation.

Drs. Takio Shimamoto, Tadao Ishioka, and Tsutomu Fujita, of the Tokyo Medical and Dental University, compared the thrombosis-preventing effects of nialamide, a monoamine oxidase inhibitor, with those of conventional anticoagulants, phenindione or warfarin, in experiments involving 121 rabbits. Following the oral administration of nialamide, nialamide plus phenindione, or warfarin to test animals, all of the rabbits, including control animals, were challenged by vascular injury. The inner walls of ear veins and arteries were uniformly lacerated with a dental hand reamer.

This challenge, report the Japanese scientists in *Circulation Research* (10: 647-657, April 1962), produced a high incidence of intravascular blood clots in control rabbits. Although test rabbits given large doses of phenindione or warfarin fared significantly better than control rabbits, by far the greatest antithrombotic effect was obtained in rabbits treated with 3 to 5 mg./kg. of nialamide. No further reduction in the incidence of thromboses was observed in animals treated with nialamide plus phenindione in effective doses. However, subthreshold doses of the two drugs, given in combination, significantly reduced arterial thromboses in treated animals as compared to their controls. This synergistic effect suggests a possibly useful method for clinical application, said the scientists.

MAO inhibitors used clinically against hypertension and psychic depression presumably alter nervous function. However, that nervous influences were not essential factors in nialamide's mode of action was shown by corollary experiments in which neither sympathectomy nor blood vessel denervation modified the antithrombotic effect of nialamide. Furthermore, nialamide, unlike phenindione or warfarin, had no direct effect on blood clotting components (prothrombin activity) involved in the conversion of fibrinogen to fibrin, the structural substance of blood clots.

Microscopic observations indicated instead that nialamide, but not phenindione or warfarin, prevented the adhesion and aggregation of blood platelets and leucocytes at sites of vessel injury. Such aggregations, the scientists explain, constitute mechanical barriers that prevent the washing away of blood-borne clotting components as well as those released locally by injured tissue and disintegrating platelets. Thus, the barriers initiate, indirectly, the formation of fibrin or "white thrombi" which, in turn, entrap blood cells and develop into full-blown thromboses.

THURSDAY, MARCH 14, 1963.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. FRANCIS A. ARNOLD, JR., DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

MRS. FRANCES H. PETTINATO, BUDGET OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	1,372	1,705	1,821
Positions other than permanent.....	42	42	42
Other personnel compensation.....	16	16	29
Total personnel compensation.....	1,430	1,763	1,892
12 Personnel benefits.....	171	201	223
21 Travel and transportation of persons.....	96	116	154
22 Transportation of things.....	10	7	6
23 Rent, communications, and utilities.....	34	61	66
24 Printing and reproduction.....	2	2	2
25 Other services.....	128	152	170
Payment to National Institutes of Health management fund.....	909	1,027	1,078
26 Supplies and materials.....	245	246	255
31 Equipment.....	153	94	74
41 Grants, subsidies, and contributions.....	9,785	13,323	15,895
42 Insurance claims and indemnities.....	1		
Subtotal.....	12,964	16,992	19,815
Deduct quarters and subsistence charges.....	6	6	6
Total obligations.....	12,958	16,986	19,809

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	234	262	272
Full-time equivalent of other positions.....	5	5	5
Average number of all employees.....	218	248	257
Number of employees at end of year.....	241	269	277
Average GS grade.....	6.5	7.2	7.3
Average GS salary.....	\$5,842	\$6,591	\$6,637

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	6,558	8,566	9,833
(b) Fellowships.....	811	1,230	1,257
(c) Training.....	2,416	3,527	4,805
Total, grants.....	9,785	13,323	15,895
2. Direct operations:			
(a) Research.....	3,131	3,005	3,200
(b) Review and approval of grants.....	344	449	529
(c) Program direction.....	143	209	185
Total, direct operations.....	3,618	3,663	3,914
Total, program costs, funded ¹	13,403	16,986	19,809
Change in selected resources ²	-445		
Total obligations.....	12,958	16,986	19,809
Financing:			
Comparative transfers to other accounts.....	2,145	2,436	
Unobligated balance lapsing.....	2,232	1,776	
New obligational authority.....	17,335	21,198	19,809
New obligational authority:			
Appropriation.....	17,340	21,199	19,809
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (-).....	-5	-1	
Appropriation (adjusted).....	17,335	21,198	19,809

¹ Includes capital outlay as follows: 1962, \$575,000; 1963, \$94,000; 1964, \$74,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$552,000 (1962 adjustments -\$5,000); 1962, \$102,000; 1963, \$102,000; 1964, \$102,000.

GENERAL STATEMENT

MR. FOGARTY. Dr. Arnold, do you have a statement for the committee?

DR. ARNOLD. Yes, sir, Mr. Chairman.

MR. FOGARTY. Go right ahead.

DR. ARNOLD. We have submitted a full statement to the committee.

MR. FOGARTY. We will put that in the record.

(Prepared statement follows:)

STATEMENT BY DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH

Mr. Chairman and members of the committee, this statement is made on behalf of the National Institute of Dental Research, to tell you what we are doing to carry out our established purpose—to investigate and study the cause, prevention, and treatment of disorders of the mouth, the teeth, and their supporting structures.

INTRODUCTION

The Institute, established in 1948 by an act of Congress and installed in its own research building at the National Institutes of Health a little more than a year ago, seeks through wide research to provide not only the newer knowledge and techniques so necessary to advance the practice of dentistry, but also the basic scientific data which can contribute to our resources in the fighting of all oral diseases, for the improvement of the general health of this Nation and of other countries of the world.

There is today a vanishing intellectual boundary in science. We cannot say or define in clear-cut fashion that here is the domain of the pediatrician; here

is the domain of the cancer specialist; here is the domain of the neurologist; here is the domain of the dentist.

Instead, we have in this research world a more generic category—the research scientist. He looks beyond the specific disease state to establish its cause. He looks beyond the causes to see what can be done by way of prevention. He identifies new disease entities. He looks at a patient not just with an eye to treatment but with an eye to total rehabilitation which involves new disciplines beyond his immediate specialty.

This identification is recognized today in the many fields of competence represented by the staff of the Institute of Dental Research. These include dentists, biophysicists, microbiologists, biometricians, cellular biologists, crystallographers, physicians, and epidemiologists.

The oral health needs of our country are great. Dental decay, periodontal disease, malocclusion, cleft palate—these are important causes of disability. Half of all tooth extractions today are due to diseases of the supporting structures. Perfectly sound teeth may have to be removed because of these conditions. By the age of 50 half our population has lost several teeth for this reason; practically everyone by the age of 65.

More than 8,000 children are born each year with cleft lip and palate. This is not just the problem of the plastic surgeon. It is a total problem. The child must look presentable, but even more important, he must be able to eat and swallow, speak clearly and distinctly. He needs to associate with other children and grow up in a normal way. The congenital factors which caused his condition need to be investigated. Dental research today is concerned with all these aspects of this condition.

A successful resolution of problems like these is dependent upon research, and research is dependent upon the availability of trained scientists who find out the new and communicate it to their fellow scientists, to practitioners, and, when necessary, to the public, so that these advances can provide effective assistance to society.

The Institute of Dental Research provides a link between the scientist and the practicing dentist and a link between the community of scientific investigators in universities and research institutions throughout this country and to some extent throughout the world. It is a unique combination of the immediately practical and the extremely fundamental.

RESEARCH ACCOMPLISHMENTS

It is to provide basic answers that the research programs of the National Institute of Dental Research have been developed. Some of these are carried out by the 86 scientists on our staff in Bethesda. Some are carried out in research institutions throughout this country through research grant funds appropriated by Congress and administered by this Institute.

In a separate document, "Highlights of Research Progress in Oral Diseases in 1962," I am providing to this committee a review of some of the work accomplished during the past year through the funds made available to us by the Congress. This represents only a small part of the total research in our area. Almost a hundred papers were published this year by Institute scientists. Several hundred others have resulted from the work of our grantees in universities and other research institutions.

During this year, each of the laboratories of the Dental Institute contributed significantly to our knowledge of the many problems of oral health and disease. These include the general areas of oral-pharyngeal development, human genetics, crystallography, protein and enzyme chemistry, and others. In these activities, our laboratories have provided a significant element of leadership to the total national dental research effort. This has encouraged research development in the universities and carries over into the sphere of dental education. As a result, our horizons today extend far beyond the walls of the Institute's laboratories and reach into the allied biomedical, physical, and behavioral science fields. It is obviously difficult to summarize all the activities that have been undertaken, but a few outstanding programs might be of interest.

FLUORIDATION

Today, some 40 million Americans are protected against early tooth decay in fluoridated water. This is based on research previously carried out by this Institute. The death in 1962 of Dr. H. Trendley Dean, who had pioneered in this

research, marked, in a way, the end of the first era in our study of dental decay. Dr. Dean, the first director of the National Institute of Dental Research, started work in the 1930's on the mottling of teeth in certain geographic areas. He learned that this disturbance in tooth formation was due to an excess of fluoride in the water used for drinking and cooking. However, he showed that this same fluoride, when present in small amounts (optimally one part per million) would protect teeth against decay without any accompanying mottling. Following these early studies, advances have been made in methods of adding fluoride to the water where it is deficient and controlling it where it is excessive. Related studies are exploring the practicality of other vehicles than drinking water (i.e., dentifrices, tablets, and ordinary foods) for administering fluorides to populations where communal water supplies cannot be fluoridated.

The long study of fluoridation in which the Dental Institute has participated is by this time familiar to Members of Congress. Final field examinations were made this year in a 17-year study on fluoridation of community water in Grand Rapids, Mich. This program, conducted in collaboration with the University of Michigan and State and local health authorities, demonstrated that water fluoridation has been practical and effective in caries control and that optimal doses of fluoride caused no mottling of dental enamel.

CALCIFICATION RESEARCH

During the past year a newly established section on crystal chemistry in the Laboratory of Histology and Pathology emphasized the study of mineralized tissue. A particularly important observation was that human bones with relatively high fluoride content tended toward crystal perfection, thereby increasing their physical and chemical stability. Since bones and teeth share some common properties, this finding may have relevance to the causes of caries and the inhibitory effects of fluoride. Of principal immediate importance is that, for the first time, direct evidence is available to show the exact manner in which fluoride may act upon biological mineral to make it more stable.

DENTAL DECAY

In some parts of the world decay is not a problem and there is no apparent correlation with fluoride content in the drinking water. For example, in parts of Alaska, dental decay is almost unknown, whereas in Iceland it is rampant. In Ethiopia, dental caries is virtually absent, but in several nearby African countries, the population is almost toothless by middle age.

Current field studies by Dental Institute epidemiologists, in collaboration with the Interdepartmental Committee on Nutrition for National Defense, are assessing the influence of nutrition on the prevalence of dental caries, as well as its relationship to periodontal disease. In these investigations a number of unusual findings have been observed and are now being analyzed by computer methods.

For example, another study of oral health among Icelandic people has been undertaken by the University of Alabama in collaboration with the University of Iceland. Iceland has a high prevalence of tooth decay and a large number of dental abnormalities, including supernumerary teeth and congenitally missing teeth. Also, dental caries seems to be more prevalent than in any other country. Pertinent to this study is the anthropological evidence that dental decay was almost absent 100 years ago. This presents a background with which to compare those current events and circumstances that might be responsible for the striking alteration in population susceptibilities.

As I have previously reported to this committee, Dental Institute scientists, in their studies of rats and hamsters over a period of multiple reproduction cycles, have, through the use of germfree techniques and other methods, shown conclusively that a specific strain of streptococcus is the cause of dental decay in the rat, and another strain causes decay in the hamster. The disease is passed from one animal to another. On the other hand, when the streptococcus is not present, the teeth do not become decayed. The principal investigators in this important research program, Dr. Paul H. Keyes and Dr. Robert J. Fitzgerald, have this year received the Albert Joachim International Prize for their work.

In an effort to carry these laboratory leads into clinical investigation, scientists at the Dental Institute have initiated collaborative studies with investigators at the Children's Haven Hospital of Lancaster, Pa., and the National Children's

Cardiac Hospital of Miami, Fla., to check groups of children who have been maintained on long-term antibiotic therapy.

PERIODONTAL DISEASE

Parallel with the expected advances in the prevention and control of dental caries, there emerges the interesting speculation that as more teeth are saved from caries, more susceptible tissue sites may be preserved for attack by periodontal disease. How realistic a forecast is this for the dental practitioner of 1970 or 1980? Since formation of dental calculus in the gingival area is recognized as perhaps the most important immediate cause of periodontal disease, systematic studies of the factors causing calculus deposition are essential. One such investigation has shown that various species of streptococci outnumber all other type of micro-organisms at all stages of calculus formation. This is contrary to the long held view that filamentous forms predominate, and may present to some a possibility that adequate measures can be found to prevent ectopic calcifications (tartar) by the elimination of suspected causative bacteria.

Another highly significant development during the year is a study which seemingly points to comparable relationships between specific micro-organisms and certain types of periodontal disease. Since the causative organism is identifiable, the eventual prospect for antibacterial measures of control is encouraging. However, a degree of reservation may be interjected because of the complexity of periodontal disease and the distinct possibility that it may in fact be several different disease entities. Supporting this hypothesis is the recent observation that, unlike caries, a certain type of periodontal disease can occur in the germ-free animal. A virus isolated from rats has been shown to cause severe periodontal disease in hamsters.

CONGENITAL ANOMALIES, GROWTH, AND DEVELOPMENT

Collaborating scientists in Copenhagen, Denmark, have invented a device to measure and graph airflow from nose and mouth during speech. It is expected that this instrument will help afflicted patients, either those who were born with cleft palate deformities or those who have problems relating to injury or disease. By comparing the airflow patterns of the patient with those of normal individuals, it is possible to modify and adjust the prosthetic appliances accordingly.

The Institute has been concerned with problems of genetics as related to the field of dentistry, since the association of oral disease with hereditary factors has long been recognized. Chromosomal abnormalities have been studied, particularly in regard to oral and facial deformities, including some forms of cleft lip and palate. Other genetic problems of growth and development are linked with such conditions as mongolism, in which dental disease is common.

Genetic studies are being carried out in populations where there have been large numbers of cousin marriages. In one such study, carried out in cooperation with the University of Michigan, the Atomic Energy Commission, and the Association for Crippled Children, Dental Institute investigators are seeking to determine the effects of inbreeding, particularly on stature, size, and dental eruption among schoolchildren in Japan. Also under study in selected populations along the eastern border of the United States are the relationships of genetic factors to cleft lip and palate, defective calcification, susceptibility to dental caries and periodontal disease. Two disease syndromes characterized by such conditions as defective speech and mucosal changes in the mouth and eyes were recently found in these people.

A new data processing program for handling the great number of variables in genetic population studies is now in use. Chromosome changes seen in certain diseases of the mouth are being investigated and cytological methods for rapid smear diagnosis of a number of oral lesions are under study.

An important experimental study this year used the drug thalidomide in laboratory tests on rats at various stages and in various dosages during pregnancy. Gross malformations of the offspring were observed, ranging from malrotation of the hind legs to palate deformities, absence of the tail, presence of extra teeth, etc. Current emphasis is being placed on the study of other prenatal factors and conditions that might be related to congenital defects.

CLINICAL INVESTIGATIONS

In clinical studies, Dental Institute scientists have developed an accurate system of age determination by microscopic examination of teeth—something of particular importance to legal medicine, but also of some importance to the anthropologists and paleontologists who study the origin and development of man.

Also under investigation have been: (1) an evaluation of new anesthetic agents; (2) determination of the effects of high-speed cutting instruments on the dental pulp; (3) problems of speech associated with oral-pharyngeal anomalies; (4) factors related to aphthous stomatitis and other soft tissue lesions of the mouth; and (5) palatal growth and development in the congenitally cleft child.

Dental Institute scientists have developed and utilized new histochemical staining techniques to demonstrate a connective tissue fiber (oxytalan) characteristic in areas of stress such as periodontal membranes, ligaments, tendons, the adventitia of blood vessels, and tissue sheaths surrounding hair follicles and sebaceous glands of the skin.

In a companion study conducted in collaboration with the National Institute of Neurological Diseases and Blindness, the Dental Institute has tested a similar stain on a series of biopsy specimens from patients with amyotrophic lateral sclerosis and found for the first time that a characteristic connective tissue disorder occurs in over 60 percent of these cases.

As you can see, this is dental research which approaches fundamental knowledge regarding the structures with which we are dealing, and the diseases which occur in these structures. The origins of disease, the prevention of disease, the treatment of disease, and the rehabilitation of the patient are all involved.

RESEARCH GRANTS

The major portion of the funds of the National Institute of Dental Research is used to develop research throughout the country. During fiscal 1963, the Institute had 425 active research grants at 138 research institutions, including all 49 schools of dentistry. These grants were made in 36 states, the District of Columbia, and 13 foreign countries.

Among the many significant studies are those of the Bowman-Gray School of Medicine, North Carolina, which is working on the genes which affect the formation of dentine and enamel; the Forsythe Dental Infirmary in Boston which has shown the relationship of fluoride in surface layer enamel to caries control; the University of Arizona which has developed a technique for determining chemical elements in dental tissues by the use of monochromatic X-ray for microradiography; and the University of Illinois which has looked further into the question whether the fluoridation of water provides protection into adult life.

New research projects have begun within the past year to develop vehicles other than the water supply for the use of fluoride to prevent tooth decay. Salt, bread, tablets, and other methods are under study to provide fluoride assistance to areas where water fluoridation is impractical or impossible. Studies of the biomedical and physiologic mechanisms of fluoridation are also under study through grants for research.

Investigations of cleft palate and other congenital anomalies of the facial region are being expanded through the establishment of multidisciplinary research centers in some of our outstanding research institutions. Maxillo-facial surgery, speech pathology, otolaryngology, prosthetic dentistry, and orthodontia are included in the scientific disciplines which share the responsibility for these studies. Through support from the Dental Institute, research will be undertaken in caries in children with clefts; the growth and development of skeletal structures; surgical, dental, and speech management; and the problems of rehabilitation.

Other important grant areas are in the fields of reconstructive materials, calcification, dental public health, and periodontal disease.

TRAINING

It is not only essential to provide for research today, but to make sure that research can continue in the years to come. Unless we train scientists, our possibilities for research will soon be limited. The Dental Institute's graduate

training program in concerned with developing competent researchers in the dental field to meet the critical shortage of clinical and basic science personnel for the future.

With the opening of new dental schools and the establishment of new dental clinics and dental research programs, the existing shortage of dental researchers and teachers trained in research techniques becomes even more acute.

There are Dental Institute training grants in 44 institutions in 22 States covering 55 different programs, and including some 200 graduate students. During the calendar year 1962, 13 new training grants were activated, and we expect that 15 more will start by July 1, 1963.

The Institute seeks to support further research training in certain areas of critical need to dentistry, not only in dental schools, but in such fields as speech pathology, physiology of calcification, metallurgy (dental materials), crystallography, and electron microscopy.

The research fellowship program is directed primarily toward graduate training in the basic sciences. During calendar 1962, a total of \$636,952 was awarded for 87 regular fellowships at 41 institutions. This was more than a 20-percent increase over the preceding year.

Sixteen research career development awards have been made during the year 1962 to finance programs for able scientists who plan to pursue careers in independent research and training.

Research career awards for more experienced investigators to provide additional stable research opportunities will be made when candidates of sufficiently meritorious standards are available.

We have received consistent support both from the American Dental Association and the dental schools in expanding training opportunities. It is our responsibility to see that the programs offered are good and that priority is given in areas where there is a particularly critical shortage. This is especially true in the basic sciences.

A committee of the Institute has been analyzing the training program in meticulous detail and has made important recommendations for its future to improve the quality of training offered and expand the number of people available for research. At the present time, the shortage of trained research personnel is one of our most serious problems.

SCIENTIFIC INFORMATION

One of the crucial areas in our program is communications. The National Institute of Dental Research has consistently sought to increase the speed and improve the quality of communications on the scientist-to-scientist and the scientist-to-practitioner level. However, we are aware of the fact that much more could and probably should be done. The Institute has helped by supporting scientific conferences, scientific journals, and similar services so that information available to the research worker could be translated as quickly as possible into programs helpful to practitioner and patient. We have long felt that the lag between research and application is too great. We would like to cut this timelag. It is obvious that research, buried in the mind of the researcher, is sterile. It must be communicated before it can fulfill its purpose.

DENTAL RESEARCH CENTERS

Dental research institutes or research centers, to be established in various parts of the country, are in the planning stage. Several sites, believed to possess the highest available potential for the establishment of such institutes, are being explored. Some of these are the University of Rochester, the University of North Carolina, the University of Washington, New York University, and St. Louis University.

Since we believe that the long-range goals of the programs should include the establishment of dental research institutes in nondental environments, preliminary discussions have also been carried out with representatives of the Mayo Clinic and the Sloan-Kettering Memorial Cancer Center. An ad hoc advisory committee will be set up to work with this program.

CONCLUSION

The biological and medical sciences in the curriculum of dental schools reproduce in many ways the research programs and curricular development seen in

the medical schools. These are closely related in a multidisciplinary complex. It is to be noted that our Institute participates in a considerable number of collaborative programs with other Institutes of NIH as well as with other research organizations. Much of this is due to the special knowledge and skills of our scientists in a variety of specialized areas such as electron microscopy, crystallography, germfree methods of research, protein chemistry and human genetics.

For the future we must plan a major attack on the overwhelming dental diseases of the American adult. Now that we are saving teeth from caries, are we preserving them for attack by periodontal disease? The prospect here is for the development of preventive measures similar to those that have been so successful for dental caries.

In conclusion, Mr. Chairman, the request for the National Institute of Dental Research in 1964 is \$19,809,000. This will provide increases to support new research projects and extend our training programs. The figures for direct research and for review and approval of grants include minor increases to strengthen ongoing programs. This request for 1964 is distributed as follows:

Grants:

Research-----	\$9, 833, 000
Fellowships-----	1, 257, 000
Training-----	4, 805, 000
Subtotal, grants-----	<u>15, 895, 000</u>

Direct operations:

Research-----	3, 200, 000
Review and approval of grants-----	529, 000
Program direction-----	185, 000
Subtotal, direct operations-----	<u>3, 914, 000</u>
Total 1964 appropriation request-----	<u>19, 809, 000</u>

Dr. ARNOLD. Due to the lateness of the hour, I will read this summary of what is in that statement.

Mr. Chairman and members of the committee:

The full statement of the National Institute of Dental Research presents an accounting of the Institute's activities in carrying out its established mission to investigate and study the causes, prevention, and treatment of diseases of the mouth and teeth.

Diseases of the oral cavity and related structures constitute a major public health problem in the United States, and one such disease, dental caries, is the most prevalent of all, affecting 90 percent of our people. A billion unfilled cavities, 6,000 new cleft palate cases each year, and periodontal disease afflicting practically everyone over age 50 are important reasons for dental research.

RESEARCH FINDINGS

This year saw significant research accomplishments to meet these problems, both in the laboratories of the Dental Institute and in the universities where grants from the Institute have been made.

A beginning was made in investigating the relationship of streptococcus to dental decay in man, based on previous laboratory findings that certain strains of streptococci cause such decay in animals. Techniques of electron microscopy and X-ray diffraction provided new knowledge of the mechanism by which fluoride protects the teeth.

Studies of periodontal disease in hamsters showed that a specific type of filamentous bacteria was the causative agent and that the disease could be transmitted from animal to animal.

Related investigations provided new information on the composition of calculus which is the most important immediate provocation of periodontal disease. A new dental material which will bond to tooth structures is being developed. Studies in the genetics and management of cleft palate have been carried forward.

Approximately four-fifths of the Institute's funds are allocated to research institutions for scientific investigation and the training of researchers.

During fiscal 1963, the Dental Institute was supporting 425 research programs at 138 universities and hospitals, including all 49 schools of dentistry. Training and fellowship programs increased by approximately 40 percent to help meet the critical shortage of clinical and basic science personnel.

A committee of the Institute has analyzed the training programs and made recommendations to improve still further the quality of training offered and to expand the number of training opportunities.

Investigations of cleft palate and other congenital anomalies have been greatly expanded through the establishment of new multidisciplinary research centers in this field. The groundwork has been laid for initiating a clinical research center program in which the relationship of oral disorders to total body health can be studied. Further intensive plans are directed toward the creation of dental research institutes to handle the problems of oral disease.

In conclusion, the request of the National Institute of Dental Research for 1964 is \$19,809,000, as compared with \$16,986,000 available in 1963. This includes increases of \$1,267,000 in research grants; \$195,000 in direct research programs; \$1,278,000 in training grants; and \$27,000 in fellowships.

I might expand briefly, if I may, Mr. Chairman.

Mr. FOGARTY. Go ahead.

Dr. ARNOLD. We have submitted, or have available for the committee, highlights of the progress that has been made during the year; and, with your permission, I would like to have this inserted in the record.

Mr. FOGARTY. Let me hear some of them. We will put them all in the record at the end of your testimony but give us three or four examples now.

RELATIONSHIP OF BACTERIA AND DENTAL DISEASE

Dr. ARNOLD. One of the interesting things was the relationship between specific bacteria and dental decay or periodontal disease.

As was previously reported to this committee, the Dental Institute scientists have studied laboratory animals, through the means of germ-free techniques and other methods, and have shown that specific strains of streptococci are the cause of dental decay in the rat, and similar bacteria cause decay in the hamster.

During this year, using special techniques, studies of periodontal disease show that various species of streptococci outnumber all other types of micro-organisms at all stages of calculus formation.

In addition to this, we have shown in the course of the year, the point that I mentioned a little while ago, that certain types of bacteria are very important in attaching this calculus or tartar to the teeth. We feel that these findings give us hope of maybe reducing the number of certain types of bacteria, such as these, and thus reduce the amount of dental tartar or calculus formed in the mouth. The end result of this should be a reduction in the amount of periodontal disease.

EFFECT OF FLUORIDE ON CRYSTALLINE BONE STRUCTURE

Going to another area, which I mentioned previously, were our findings in electron microscopy of the chemistry of the teeth.

We have found that the element fluoride, an element about which we have spoken to you at considerable length over the past many years in terms of its relationship to the fluoridation of the water supply, we have found that the element fluoride increases or improves the crystallinity of the structure of bones, namely the apatite structure of bone tissues.

The apatite structure of bone tissues is quite similar and comparable to the structure of the enamel and dentin of our teeth.

It is highly possible, and probable, that one of the methods by which fluoride in water supplies decreases tooth decay is through the formation of a more perfect crystalline structure of the enamel and the dentin of the teeth.

I think there is another interesting aspect to this. It does suggest some potentiality of fluoride as related to certain bone diseases, such as osteoporosis. There is evidence in the literature that fluoride is being used to reduce the general disease condition of osteoporosis, where, particularly in older age and during certain periods of menopause, the bones of individuals appear to erode away.

This is a serious disease. While we are not studying it, and Dr. Whedon may tell you more in terms of the studies at the Institute of Arthritis and Metabolic Diseases—we think this finding is a very interesting phenomenon.

CLEFT PALATE RESEARCH CENTERS

One of the other areas the committee has been interested in is cleft palate. We were encouraged last year to increase our activity in the field of cleft palate research. We had established one center for cleft palate research studies, namely at New York University.

Since that time, and before the end of this year, we will have established four more cleft palate centers for studies in this area, namely in Rochester, N.Y., at the University of Pittsburgh, in Iowa, and at Duke University.

We have now under negotiation or discussion, five other universities, in terms of their ability to establish cleft palate clinics in those universities.

During the year, we also have had under discussion the potentiality of establishing in this Nation some broader dental health centers or dental research institutes, as we have called them. We have discussed this matter with the officials, the administrative officials, of several of our health center complexes in this country. We feel that

there is the opportunity to expand dental research and get some strong research centers operating in four or five schools related to some of the larger health centers in our Nation.

We are hoping that within the next year one or two of these might be started.

That covers briefly some of the activity, Mr. Denton.

Mr. DENTON. Thank you.

Dr. ARNOLD. I will be happy to answer any questions.

Mr. DENTON. The 1963 appropriation, adjusted for comparability, is \$18,762,000, and the request for 1964 is \$19,809,000, an increase of \$1,047,000.

BUDGETARY RESERVES

However, since there is a reserve of \$1,776,000, the budget proposes an increase in spending of \$2,823,000.

What is the explanation of this reserve?

Dr. ARNOLD. Mr. Denton, do you mean the unobligated reserve?

The explanation of that is we were not able in our grant program—we did not have enough approved applications to use up the total appropriation that was given to us by the Congress last year.

It refers to the same reserves that come up in the other budgets.

Mr. DENTON. That means you will either have to obligate that before the first of the year, or it reverts to the Treasury?

Dr. ARNOLD. That is my understanding.

Mr. FOGARTY. You have a reserve of \$1,776,000. How much of that was in training?

Dr. ARNOLD. About \$492,000 is in training.

Mr. FOGARTY. Do you have the same problems that Cancer and Heart have? The Mental Health Institute is different than the others regarding the training program. But it seems to me that you would be in the category of the Mental Institute rather than Heart and Cancer. How do you feel about that?

Dr. ARNOLD. Mr. Fogarty, I think we are in a position like maybe some of the other Institutes, in our training. As of the time we put these reserves aside, we didn't feel we would be able to get all our training program into operation. That is the total amount that was there.

At the present time, under the reserves that we have shown here, we will have an anticipated deficit of some \$225,000.

This can be covered by transfers of funds in our research grants program, and we have not asked at this time for funds to be released from this reserve.

Mr. FOGARTY. Why not get the reserve lifted?

Dr. ARNOLD. Because we have money left in our clinical center—money that was earmarked for clinical research centers—\$350,000 that was not expended this year. We have not had applications.

Mr. FOGARTY. Why not take it out of the reserve of \$492,000 instead of transferring it? Is that more difficult to do?

Mr. KELLY. It is our plan, as I understand it, when the March Councils are over and we know what projects are approved, and how it relates to the funds, to make a reassessment.

As Dr. Arnold said, the amount of money apportioned to him may be adequate to cover all of his needs, but it may be in the wrong pockets, and we will work out a redistribution.

Mr. FOGARTY. It was brought out that this is very seldom done—this transferring.

Mr. KELLY. This really wouldn't be the same transfer. It wouldn't be the transfer of a budgeted item. It would be that he had reserves in both categories.

Mr. FOGARTY. When will you know about the March Council meeting recommendations?

Dr. ARNOLD. I left the council this morning to come down here. They are supposed to finish at 1 o'clock today, according to the agenda, and we will know within the next week.

Mr. KELLY. For the total—we will get the sum added up—I will suggest it would be the end of the first week of April.

Mr. FOGARTY. I would hope that it would not be any later than the middle of the first week of April.

Can you not make sure that you have this information to us by the 4th or 5th of April?

Mr. KELLY. I think we could; and we will see that we do.

TRAINING PROGRAM

Mr. FOGARTY. I do not think I got the answer to my earlier question. I think that you are in the same category as Mental Health, as far as training is concerned, rather than having the problems Cancer and Heart have.

From the explanation by Dr. Shannon and Dr. Endicott yesterday, it seems to me that that would be the situation.

Mr. KELLY. Certain service-type training in the Dental Institute was, in this year's budget, transferred to Community Health, so that they are more similar to Heart and Cancer in being related only to research training in the Institute and having the service training in the Bureau of State Services—is that not right, Dr. Arnold?

Dr. ARNOLD. That's correct. Money we put into our graduate training program was spent, and we have the \$225,000 that is our estimated budget as of today. That would come out of the reserve for grants.

Mr. FOGARTY. Maybe I did not ask the question right. You are in the one field of dentistry and not, like Cancer and Heart, in a multiplicity of other related areas. Is that right? You are just training in dentistry.

Dr. ARNOLD. That is correct; and I thought of that when Dr. Felix was testifying this morning. Some of his problems and our problems are similar in terms of a narrow field.

Mr. FOGARTY. What do you say, Dr. Shannon? I think this ought to be clarified a little more, because of your statement earlier, because of the difference between Dr. Felix' Institute and Dr. Endicott's.

Dr. SHANNON. I think some of the problems of this Institute parallel those of the Mental Health Institute.

This Dental Institute money represents almost the total money going into dental research or dental research training in the entire country. There is a similar relationship between Mental Health Institute funds and the funds for health research and research training in the country. This is not true of other areas, such as cancer, heart, and the like.

But my analysis of the problem, which I will give you in just a moment, has led to some fairly drastic suggestions for program changes within the Dental Institute program.

Some of these have been accepted, and are being implemented in the present year.

I think the key to the whole problem is that in the dental area, after research programs have grown over a number of years, it becomes increasingly difficult to find truly meritorious new proposals by which to expand beyond existing program levels of about \$20 million.

This is the measure of the total number of scientists engaged in research in this country with direct relevance to dental problems.

POSSIBLE CHANGES IN PROGRAM

Now, sometime last spring I discussed with Dr. Arnold the possibility of breaking the previous mold of his research support, which was mainly in the form of small grants, made primarily within schools of dentistry or associated laboratories. Instead, I suggested an attempt to set up research institutes in the dental sciences in some four or five or six locations throughout the Nation. These institutes would be comparable in size and analogous to the one that Dr. Arnold runs at Bethesda.

I further suggested that these dental research institutes might better be set up within a general university environment rather than as part of a strictly dental school complex.

I think that some large measure of the success of the National Institute of Dental Research is due to the day-to-day association with a broad range of scientists whose work relates at one point or another to some aspect of the dental programs.

I pointed out to Dr. Arnold that if his Council agreed, the setting up of several dental research institutes was a logical step in program development, and that a whole array of devices could be used for this purpose. I said I would talk to the Research Facilities Resources Council, and that Council members are quite willing to give special consideration to the need in this area. While there would be no earmarking of funds for construction, Council members said that if they were presented with a sort of package-related deal, they would give high priority to consideration of this particular need.

We pointed out that the shortage of scientific personnel in the field might be broken in part by providing adequate facilities for research. At the present time research facilities represent the most limited of all the components of the program. Improved facilities certainly would ease recruiting problems.

In connection with setting up these new research institutes, it would be possible to negotiate for positions under the career development award program. This would provide them assurance of a certain amount of personnel support there, and even provide some assurance that suitable people would be obtained for a limited but adequate number of awards.

General research support grants and training grants might also be used to make it more attractive for universities to get into this area.

Now, it is my personal conviction, and I am glad that the Dental Council and Dr. Arnold generally agree, that it is this type of ap-

proach that will break the mold of the past, broaden research in the dental sciences, and provide adequate training spots for true scientists within the profession. I think this approach would have a profound impact on dental research activities in as little as 5 years.

But, Mr. Fogarty, I am convinced that in the absence of some such new approach as this, scientific leadership in this area will not be developed, nor will we really have a science plan that can seriously address itself to the main problems of dental research.

I have not talked to Dr. Arnold about this in terms of presenting it to this committee. What I am proposing is a simple adaptation of the multiple devices for improvement that we already have, to the particular situation now existing in the Dental Institute, for I know that Dr. Arnold is not entirely satisfied with the way his program is evolving, either in its qualitative or quantitative aspects. It is necessary, I believe, to extend our efforts beyond the strict limits of the dental school, as it is presently constituted.

If Dr. Arnold disagrees, I hope he will say so, because we have not discussed this prior to presenting this line of thought to the committee, Mr. Fogarty.

It is not a new program that I am suggesting here; rather it is an assemblage of elements from a number of programs, that can help us in solving our specific problem.

Mr. FOGARTY. Go ahead, Dr. Arnold, tell us what you think about this.

Dr. ARNOLD. I would like to comment on that.

We have met and I have visited with the administrative people of six of our larger university complexes to date. I think that they are, in most instances, quite interested in what they can do in bringing dentistry and dental research into the health centers that they are building in these institutions.

There are certain problems that we have in this regard. One is, at the present time, the shortage of scientific manpower in dentistry to develop these things. We are competing for the same type of manpower that all the institutes are competing for.

I think that our training programs within the next year or two will be turning out an increased number of persons to help alleviate part of this problem.

The second problem that we run into, in talking to the administrators of the universities, is the problem of construction, the construction costs.

I think I have reported to you before that there have not been, in dentistry or available to dentistry, matching funds. I think that the budget that is presented in total NIH here shows that out of the \$230 million that has been appropriated and gone into construction funds, slightly less than \$3 million has been earmarked and gone into dental schools.

The principal problem has been that the dental schools have not had their matching funds.

In discussing it with the dental school people, they feel that the university may be holding back, hoping to get total construction funds.

There is no question that our dental schools need construction funds throughout the country.

Mr. FOGARTY. I agree with you.

TENDENCY OF DENTAL SCHOOL NOT TO HAVE SEPARATE RESEARCH BUDGET

Dr. ARNOLD. The third problem I have run into is, by tradition, habit, or otherwise, dentistry has never had a separate budget for research, per se. In many cases the budget for dental schools is entirely related to teaching, and is entirely related to the number of students you have to teach, and very little money has even been earmarked for research.

Fortunately, in visiting the two new schools—namely, at Lexington, and the one that is underway at the University of California in Los Angeles—both of these schools are budgeting money for research, shall we say, more or less full-time research personnel, a practice which is common in health centers and in the medical schools.

Thus, there is another problem in this regard, and that is the problem of some system where we can help them develop such research programs.

At the present time, under our authorities, under our present grants system, it is difficult to help some of these schools at the proper time. This is particularly true, I think, of some of the newer schools that are now recruiting personnel. They have no true pocket of money to go out and recruit a particular man, because he is already, shall we say, on a grant or other project. To move him and put him on your staff, it is a good year before you can build up his laboratory, his equipment, and have his projects in operation at the new school.

This is one of the problems I have run into in the schools, at least this is what they tell me is their problem.

Whether there are potentialities of further extension of the authorities and use of general research support grants—and I have not discussed this with Dr. Shannon yet, either—to do something along this line, I do not know.

But I think you must realize that taking the example of our two new schools, they have a base grant of only \$25,000 and \$25,000 to do this does not go very far. This is not what they have to have, but this is what they have available to them to start recruiting people and get them working at their organization.

Mr. FOGARTY. Did you disagree with anything Dr. Shannon had to say?

Dr. ARNOLD. No, sir; I did not disagree with anything he had to say.

Mr. FOGARTY. I think that is one of the best statements I have heard for dentistry in a long time.

This suggestion that Dr. Arnold just made, do you have any fault to find with it, since he did not have a chance to discuss it with you?

Dr. SHANNON. No.

The point is we have all the authorities to do all of these things, but there is no point in moving ahead until we have sufficient agreement in a number of areas we know the program should go in.

I would not propose to program dollars on the vague hope that this program might come into being. But if Dr. Arnold can get a number of university centers very seriously interested, then we would propose the program; we would propose the dollars. We have all the authority we need.

ESTIMATED COST OF POSSIBLE NEW PROGRAM

Mr. FOGARTY. All right, what would this Shannon plan cost? About?

You can figure this up when you get a chance to think it over.

Dr. SHANNON. We can give you a figure.

Mr. FOGARTY. What would you think?

Dr. SHANNON. This would require about a 5-year development period. To create the type of installation we are talking about would take about \$4 million in construction funds for each center.

For six centers across the Nation, we would need about \$25 million expended over a period of 3 or 4 years.

I would say one would have to use the general research and training authority in a special way. This idea, I believe, is there in the legislative history, in the basic authority; but money has not been asked for in this manner. It would involve using about a quarter of a million dollars for the next 4 or 5 years; and then tailing off during the subsequent years, for a 10-year cycle.

To get these things going at six schools would require spending about \$1.5 million, in round figures, in support grants.

I think, in the aggregate, it is not going to cost NIH any more to tackle dental research in this manner. It is going to bring to the solution of dental research problems people who will seriously address themselves to those problems.

To make real use of six centers, you would have to provide up to around \$150,000 to \$200,000 a year, in terms of training grants, to support training staff and to provide stipends.

But with relatively small funds, you could bring into being, over a period of 5 years, a really significant program in the dental sciences.

Mr. FOGARTY. I think you mentioned at the beginning of your statement that there has been a considerable increase in your appropriations since 1954. For 1954 your request was cut almost a million dollars. For 1955 it was increased from your request for \$1,730,000 to \$1,990,000. Then for 1956 you requested \$2,136,000 and Congress appropriated that amount. In 1957 the request was \$2,971,000 and Congress appropriated \$6,026,000. In 1958 you requested \$6,430,000 and Congress appropriated that amount. For each year since then Congress has increased the amount gradually up to \$21,199,000 for 1963.

It has been a fairly gradual increase, so far as the total appropriations are concerned.

Dr. SHANNON. I am not suggesting this be modified at this point in time, because I think actually if you markedly expanded this area, Dr. Arnold would have difficulty in utilizing the funds.

On page 263, Mr. Fogarty, as you see in the aggregate, in this fellowship program, the Dental Institute attributes only nine people in predoctoral training.

Now, on the subject, it takes 5 years to train these people; that means they are contributing to the manpower pool about 2 men per year.

My feeling is that that type of contribution is never going to change the fate of dental research in this country.

GENERAL RESEARCH SUPPORT GRANTS

Mr. FOGARTY. I visited the new dental school at the University of Kentucky. I received this letter from them recently. I will put the whole letter in the record, but I will get down to the pertinent part:

As a new dental school, we are dedicated to the launching of a vigorous research program with minimum delay. No doubt you are familiar with the several mechanisms available to dental schools for acquiring research funds and the fact that such mechanisms, though effective, are functional at the expense of time. Stated otherwise, we are able to obtain funds after faculty members are recruited and after research proposals have been prepared, submitted, reviewed, and approved. At this rate, we shall be able to achieve our maximum research potential sometime within the next 5 to 10 years, if we are fortunate. It is our opinion that this rate of progress can be accelerated, indeed it should be, if we are to meet the needs and challenges of American dentistry.

It is generally known that the National Institutes of Health initiated the awarding of general research support grants, at the rate of \$25,000 per year, in order to make available to medical and dental schools an amount of money that could be expended to support new research within the schools' discretion concerning the use of such funds. We have been fortunate in receiving such grants in 1962 and 1963, and deeply appreciate such support. However, for our needs—to move from scratch rapidly into a vigorous research program—a sum of money in the order of 10 to 20 times the amount available via the general research support mechanism is required.

As a dental school seeking Federal research support, we quite naturally turn to the National Institute of Dental Research as the first source for assistance. Unfortunately, NIDR is not authorized to grant more than the \$25,000 mentioned above in general support, the type of assistance most needed by us at this time in order to launch new research. This situation is particularly frustrating to dental research in view of the possible availability of unexpended extramural research funds.

That is the gist of the letter. I will put the whole letter in the record. It was signed by Alvin L. Morris, dean of the new Medical Center, College of Dentistry.

(Letter is as follows:)

UNIVERSITY OF KENTUCKY,
COLLEGE OF DENTISTRY,
Lexington, Ky., March 1, 1963.

HON. JOHN E. FOGARTY,
House of Representatives, House Office Building,
Washington, D.C.

MY DEAR MR. FOGARTY: Your effective leadership in fostering legislation dedicated to the Nation's health prompts me to communicate with you about the future of our college of dentistry. You will recall your important role in the dedication of our college in Lexington last September and the fact that our college is an integral component of a health center. As such, we enjoy an especially advantageous position in being able to collaborate with medical research scientists as well as workers in the basic science fields. Thus, since your visit we have devoted much attention to the initiation of a major research program and it is about this matter that I am now addressing this letter to you.

As a new dental school, we are dedicated to the launching of a vigorous research program with minimum delay. No doubt you are familiar with the several mechanisms available to dental schools for acquiring research funds and the fact that such mechanisms, though effective, are functional at the expense of time. Stated otherwise, we are able to obtain funds after faculty members are recruited and after research proposals have been prepared, submitted, reviewed, and approved. At this rate, we shall be able to achieve our maximum research potential sometime within the next 5 to 10 years, if we are fortunate. It is our opinion that this rate of progress can be accelerated, indeed it should be, if we are to meet the needs and challenges of American dentistry.

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could be expended to support new research within the schools discretion concerning the use of such funds. We have been fortunate in receiving such grants in 1962 and 1963, and deeply appreciate such support. However, for our needs—to move from scratch rapidly into a vigorous research program—a sum of money in the order of 10 to 20 times the amount available via the general research support mechanism is required.

As a dental school seeking Federal research support, we quite naturally turn to the National Institute of Dental Research as the first source for assistance. Unfortunately, NIDR is not authorized to grant more than the \$25,000 mentioned above in general support, the type of assistance most needed by us at this time in order to launch new research. This situation is particularly frustrating to dental research in view of the possible availability of unexpended extramural research funds.

To accentuate our particular frustration, you may recall that we have research space available in our new dental school to accommodate about 15 senior research investigators. We believe our research objectives would be considered sound by a board of scientific peers. Finally, in spite of a feeling in numerous circles, implying that dentistry cannot attract competent research talent to this area of health research, we feel confident that we will be able to staff our research program. Thus, what is needed in our situation is monetary support, money which is available for research within the Federal Government's planned expenditures, and yet money that cannot be unleashed because of the lack of appropriate mechanism of funding.

Of course, we intend to take the fullest advantage of the present fund granting mechanism, but such procedures hardly provide a vehicle for launching a broad research program such as can be conceived for a dental research institute. The greatest loss under the existing mechanism is time, the priceless ingredient for progress.

It is our understanding that you and other Members of the Congress will be deliberating over such matters in the near future. We respectfully invite your attention to the type of situation described above, one which will typify the research plight of other dental schools now being planned and intended to meet the needs of American dental health. Your interest in these matters is sincerely appreciated.

Warmest personal regards,
Sincerely yours,

ALVIN L. MORRIS, D.D.S., Ph.D.,
Dean.

Mr. FOGARTY. Now I would think an area like this, with one of the most modern schools of dentistry in the country, maybe in the world, is an area where some exception of some kind ought to be made.

Dr. SHANNON. I do not think he overestimates the need. He says \$250,000. I mentioned a grant of a quarter of a million dollars. So we are pretty much seeing eye to eye about the amount of money that is necessary to get a program of this sort underway.

On the other hand, I think the University of Kentucky Dental School is in a very unique position at the present time, to do this; and the question is: Does one start a new program on the basis of one opportunity?

I think we would be quite prepared to support a program of this sort if Dr. Arnold can generate the interest to make it a truly national program, facing up to a national need.

Mr. FOGARTY. I am not going to interfere, of course, with the established procedures. But it seems to me, and I have talked to you about this, and I think we all agree, there are some medical schools that ought to just be torn down and rebuilt from the ground up.

Dr. SHANNON. Yes.

Mr. FOGARTY. It is going to take a long time before they are in the position that Kentucky is in now.

Dr. ARNOLD. To do this.

Mr. FOGARTY. Maybe you should take a look at this overall situation, and come up with something that might take care of the problem that this university is having.

Dr. ARNOLD. May I comment?

Mr. FOGARTY. Sure.

Dr. ARNOLD. As I mentioned, the two new schools are in this position. There are a number of other schools in this country that might be in this position. They have their laboratories and places for their people. It is a question that they need, as I call it, a developmental or an add-on to their general support grant. This can be done within the grant funds.

As Dr. Shannon pointed out, if he would get this program, taking Kentucky as an example, there are other programs for support, such as career development program and project grants.

Mr. FOGARTY. Oh, I am not for deleting any other programs to take care of this. I just assumed that Dr. Shannon was going along with your ongoing program, and this is in addition to what you are already doing. Right?

Dr. SHANNON. Yes.

Mr. FOGARTY. That is the way I understood it. Is that not the way you understood it?

Dr. ARNOLD. I said I had not had the chance to discuss this with Dr. Shannon.

Mr. FOGARTY. I know, but you listened to him just now.

Dr. ARNOLD. I do have these three problem areas in getting these centers started.

LETTER FROM PAST PRESIDENT OF THE A.D.A.

Mr. FOGARTY. I received a letter from the past president of the American Dental Association and dean of the School of Dentistry at the Medical College of Virginia.

His first paragraph was:

Pursuant to our recent conversation, I am pleased to set forth some thoughts regarding the possibility of establishing one or more regional dental research institutes or centers.

Is that what you are referring to?

Dr. SHANNON. We have a dental school to be added sometime this fall.

Mr. FOGARTY. This is the dean.

Dr. SHANNON. I think he was on the executive committee that came in.

Was he not one of those that met us?

Dr. ARNOLD. I believe Dr. Lyons was; yes.

Dr. SHANNON. So he is well aware of the capabilities of this, to do the job they want done.

But he also, at the time we talked, was well aware of the intensive job of programing that will be required on an institution basis to come up with a sound proposition.

Mr. FOGARTY. Oh, I would agree there.

He said:

The cost factor for construction might be in the range of \$1 to \$3 million.

I will put the letter in the record.
(Letter is as follows:)

MEDICAL COLLEGE OF VIRGINIA,
SCHOOL OF DENTISTRY,
Richmond, Va., December 17, 1962.

HON. JOHN E. FOGARTY,
U.S. Congress, House of Representatives, Washington, D.C.

DEAR MR. FOGARTY. Pursuant to our recent conversation, I am pleased to set forth some thoughts regarding the *possibility of establishing one or more regional dental research institutes or centers.*

It is my understanding that the high level administrators of the National Institutes of Health hold the opinion that the Institutes and their programs at Bethesda are now as extensive as they should ever be, with due regard to their effective management and efficiency. I have been advised that, in their judgment, further expansion should be developed in terms of regional institutes or centers. The director of the National Institute of Dental Research has expressed a firm opinion on this score.

The establishment of regional dental research institutes or centers should, in my judgment, be based on a plan involving the pursuit of dental research in specified categories. For example, a regional dental research institute might be established for research activities related to the realm of the periodontal diseases or to genetics in relation to dental disease. On this principle research could be more effectively organized and directed to the end that better coordinated efforts would be more productive. This is an important consideration when viewed in contrast to the numerous unrelated research projects which are now supported on an extramural basis.

It appears desirable that regional dental research institutes be established on university campuses or in health centers which include dental schools, and in an environment where extensive research in other fields of health is being pursued. The advantages which would accrue from the latter and from an academic environment would be significant.

The facility to house a regional institute should be adequate for a broad multidisciplinary research program. I know of no school which can now offer this type of physical facility, and I doubt that matching money for this purpose would be made available by universities, in light of their pressing needs for educational facilities. Accordingly, I am expressing the hope that the National Institute of Dental Research may be able to contract with the parent institute of a dental school for construction of an adequate facility provided that a site is afforded and that the school offers other prerequisites such as competence in management, research direction, etc. I would be grateful to you for your inquiry regarding the legality of this approach to the establishment of a regional dental research institute.

The cost factor for construction might be in the range of \$1 to \$3 million. The magnitude of such a venture is obviously one that indicates the necessity for support from our Federal Government.

Sincerely,

HARRY LYONS, *Dean.*

MR. FOGARTY. But is this in accordance with your thinking?

DR. SHANNON. Yes, sir; except, I think, if he is talking about total construction——

MR. FOGARTY. This is dated December 17, 1962.

DR. SHANNON. Then this is after we met with him. He was one of the consultants of the ADA who met with us. One of the problems here is that if he builds something between \$1 and \$3 million, he will not get above the critical mass of the existing research environment.

These buildings will cost around \$4 million to build and equip. If you are really going to set up a center that is going to serve on a regional basis and bring stimulus to an entire area, you cannot build it for less than that.

I would say that one of our problems is that the universities do not realize that the same factors apply to dental research that apply to anything else.

Until you get up to a critical size, you do not get too much for your money.

Mr. FOGARTY. I understand. I agree with you on that.

Dr. ARNOLD. May I make a comment on that?

Mr. FOGARTY. Yes.

Dr. ARNOLD. I have discussed this with Dr. Lyons, too, when I saw him at the deans' meeting. He has a little different concept which I would like to point out for the record.

His concept is to build a regional center for periodontal disease, per se. He does have a different problem than they have in Kentucky, because, as I say, he does not have laboratories. He needs construction, he needs the whole thing.

Mr. FOGARTY. What specific problems have you encountered in your efforts to develop good dental research centers outside of the NIH?

Dr. ARNOLD. As I said, the three major areas of the problems are the manpower problem, which is being taken care of; the lack of matching construction funds in dental budgets; and the concept that you got in your letter from Dr. Morris on the subject of a pocket of money, such as the general research support grant, to get these programs in operation.

ACTION NEEDED TO GET DENTAL RESEARCH CENTERS ESTABLISHED

Mr. FOGARTY. What do you think needs to be done to stimulate establishment of dental research centers in some of the dental schools?

Dr. ARNOLD. I do not quite know how to answer, other than what we are doing. At the present time we are out discussing it, as Dr. Shannon pointed out, not only with the dental school but with the university complex that surrounds that dental school.

I feel that in places I have gone they are willing to proceed with trying to build and set up centers in these different areas.

The two major problems I run into are the need of funds in dentistry to develop a program; and the other one, as Dr. Lyons pointed out, that while he has a relatively new dental school in terms of a teaching institution—and it is a well-constructed one—at the present time the funds come from his legislature. I think his school is about 5 or 6 years old, and he cannot go now and get matching funds to build a research wing onto that school. That is what he is planning to do.

Dr. SHANNON. He is going to build two, I understand.

Mr. FOGARTY. Would it help to increase the general support grants that are now available?

Dr. ARNOLD. That is one mechanism that could be considered; I was speaking of developmental grants. I do not know that that should be done across the board, and I do not know that it needs to be done across the board; but I think there are some of these schools that could have an increase in their general support grant.

That has many complications, and I would like for Dr. Shannon to speak to that.

Dr. SHANNON. Mr. Fogarty, we have discussed this at great length, and we feel we cannot support a general increase in support grants in order to achieve these limited, isolated objectives; nor would we be willing to simply increase general support grants to individual schools.

On the other hand, if this is part of the broad program that most

certainly will achieve the objectives, then we are quite willing to go forward and support the general program very vigorously.

I do not believe we have the information today from dental schools or from universities with favorable orientation toward dental problems that would warrant us making the request at this time. We are hoping that this information will become available in time for the preparation of next year's budget; but that information is not available today.

RESEARCH GRANTS PROGRAM

Mr. DENTON. Now, your increase is about equally divided between research grants and training grants. Like so many others, your budget calls for a leveling off of the research grant program.

You are budgeting for 111 new grants in 1964, and that is exactly the number to be financed in 1963; is that right?

Dr. ARNOLD. That is correct, sir.

Mr. DENTON. Do you not think you will have more applications next year than this year?

Dr. ARNOLD. Mr. Denton, you are talking about the 111 new grants which were budgeted?

Mr. DENTON. Yes.

Dr. ARNOLD. \$2,642,000 each year.

It is our estimate that the number of new grants will not increase during this coming year.

There are increases, of course, in continuation grants. Grants that we start this year will become continuation grants next year.

Mr. DENTON. How many applications do you have pending?

Dr. ARNOLD. We have pending at the present Council meeting 75 or 76 applications. [Corrected to 87.]

Mr. DENTON. How many have you granted this year to date?

Dr. ARNOLD. We have granted totally, that is continuation and new, around 450.

Mr. DENTON. And you have money for how many of the 76?

Dr. ARNOLD. We estimate we will have enough money to cover the 76; and we expect a balance of \$108,000. This is part of the balance I said might be used for the——

Mr. DENTON. Would the \$1,776,000 enter into that?

Dr. ARNOLD. No, sir.

Mr. DENTON. Besides that, you will have \$108,000 additional?

Dr. ARNOLD. Of the portion of the programmed funds, we had \$108,000 prior to this Council meeting; and when we prepared these data, we did not see that we would have approved applications to pay using that——

Mr. DENTON. So you will have \$108,000 in addition to the \$1,776,000 to revert to the Treasury?

Mr. KELLY. Not necessarily, Mr. Denton. We were talking to the chairman, and promised to give him a report early in April.

The figures that are in the budget, of course, are the estimates we made early in the year, when we apportioned the funds. Now as to how much will be left over, we will give you an assessment of that on the basis of the March Council actions.

POSSIBLE TRANSFER TO TRAINING GRANTS

In this instance, Dr. Arnold has more money left over, it now appears, than we thought would be left over in research grants; but he also has more approved applications in the training grant area than we anticipated. So that this will be a part of the reassessment.

Mr. DENTON. How many applications for training grants do you have that you do not have enough money for?

Dr. ARNOLD. There are \$225,000 worth; an estimated \$225,000 worth. Estimating the figure, that would be about four grants.

Mr. DENTON. How many?

Dr. ARNOLD. Four. I am taking average training grants. I do not know which ones these would be.

Mr. DENTON. How much are you short on the training grants?

Dr. ARNOLD. \$225,000 our estimate is as of now.

Mr. DENTON. I see.

Now, do you intend to transfer this research grant money over to training?

Dr. ARNOLD. We are intending to request such a transfer; yes, sir.

INCREASE FOR BROADENED TRAINING GRANT PROGRAM

Mr. DENTON. Now, you have an increase of \$1,278,000 budgeted for training grants. On page 270, you say you plan "to initiate an experimental training program in a few schools." Would you describe this new program, and tell us what the cost will be?

Dr. ARNOLD. The new program that we are initiating is to take a new school and get a sophomore, possibly a freshman student, to change his course of study so that he will come out and prepare himself more thoroughly in basic sciences, and then take his clinical and basic sciences together over a period of 6 years, in which case he will graduate with both a dental degree, and either a Master's or Doctor of Philosophy degree in some basic science.

Mr. DENTON. What will the program cost?

Dr. ARNOLD. The program, as we estimate it, can be operated under our existing program of fellowships and training as we have them here. It would be a supplement to a training grant.

Mr. DENTON. You are going to take it out of your present training grants?

Dr. ARNOLD. That is correct.

Mr. DENTON. And could you tell us how much it would cost, how much you take out of that training grant?

Dr. ARNOLD. You mean per individual?

Mr. DENTON. For this special program, yes.

Dr. ARNOLD. Per individual, our estimated cost would be about an additional 3 years, which would be an additional \$30,000 over a period of 3 years. It would cost about \$10,000 a year per student; and we are actually supporting him and extending training for a period of about 3 years.

Mr. DENTON. The \$10,000 per trainee?

Dr. ARNOLD. Per trainee.

Mr. DENTON. How many would you grant this time?

Dr. ARNOLD. At the present time we have granted none. We have one request in to do this, which includes two people. It includes stipends for two individuals.

Mr. DENTON. That would only be \$20,000?

Dr. ARNOLD. That would only be \$20,000; yes, sir. And we have planned within our increases in the 1964 budget to absorb this type of a program.

Mr. DENTON. How would the rest of the increase for training grants be spent?

Dr. ARNOLD. In our regular graduate training programs, in both dental schools and in basic science departments throughout the country.

GERM-FREE ANIMAL RESEARCH

Mr. DENTON. I do not know whether you discussed this or not, but have you discussed research with germ-free animals?

Dr. ARNOLD. Only briefly.

Mr. DENTON. Do you want to say something more about that?

If you would rather put it in the record, you can do it.

Dr. ARNOLD. I would be very happy to put a report in the record on germ-free animals.

(The information follows:)

GERM-FREE ANIMAL RESEARCH

The use of germ-free animals in research is a relatively recent development. These animals, reared in a world without bacteria, are born free of germs, eat germ-free food, drink germ-free water, and breathe germ-free air. They are contributing markedly to our knowledge today because scientists can study the effect of single types of bacteria on the life processes of an animal without the interference of the many other types of bacteria which normally flourish in the body of every animal.

Several kinds of germ-free tanks have been devised for carrying on this type of research, the most commonly used being the Reynier tank, which is a large steel tank with glass observation windows. Long sleeved rubber gloves are attached to holes in the side of the tank, and through these the scientist can handle animals from outside without contaminating them. Food, specially processed, is introduced through double-door locks and sterilized. It is removed from the lock by the scientist in his rubber gloves.

The National Institute of Dental Research has a large laboratory of germ-free tanks in which studies are made on the biology of animals grown in this special environment. Dr. Robert J. Fitzgerald, the director of this laboratory, has recently reported on the contribution which this type of research has made to dental health. A reprint of Dr. Fitzgerald's report follows. Dental Institute studies in germ-free animals includes dental caries, dental calculus and periodontal disease. The implications of these studies are now being followed up in human populations in several parts of the country.

GNOTOBIOTIC CONTRIBUTION TO ORAL MICROBIOLOGY

By Robert J. Fitzgerald

(National Institute of Dental Research, National Institutes of Health, Public Service, U.S. Department of Health, Education, and Welfare, Bethesda, Md.)

The term "gnotobiote" was coined by Prof. James A. Reyniers and his colleagues¹ at the Lobund Institute of the University of Notre Dame to describe the biologic status of the animals used in germ-free research. Because it is manifestly impossible to guarantee with certainty that a "germ-free" animal is indeed free of every form of microbial life, the term "gnotobiote" was deemed

¹ Reyniers, J. A., Trexler, P. C., Ervin, R. F., Wagner, M., Luckey, T. D., and Gordon, H. A. The Need for a Unified Terminology in Germfree Life Studies, *Lobund Rep.*, No. 2, p. 151. Notre Dame: Indiana University Press, 1949.

more appropriate, since, etymologically, it refers to an animal with a known microbiota. Stated in another way, the term implies that an animal is "germ free" within certain specified parameters determined by the type of tests made for the presence of microbial contaminants. Thus, for example, an animal may be demonstrably free of detectable bacteria, yeasts, fungi, and protozoa, but, unless specific tests were also made for viruses and rickettsiae, one would not be justified in concluding that the animal was, in fact, germ free.

As a logical extension, the "gnotobiotic" would also include germ-free animals deliberately inoculated with one or more known types of microbes for experimental purposes. Finally, one might stretch the definition still further to include animals that might harbor a normally complex microbial population but that lacked one or more specified types of organisms. It is felt that all these conceptions of the term "gnotobiotic" are valid and appropriate to the subject of this discussion, and consequently the term will be used in this discussion in its broader connotation.

The fact that the oral cavity is one of the most densely populated parts of the body, from the standpoint of microbial inhabitants, has long been a deterrent to the discovery of the causes and, therefore, the means for complete control of oral diseases. Simply because of the number and variety of microbes at any given disease site in the oral cavity, it has been virtually impossible to say which, if any, of the organisms present was etiologically related to the disease in question.

DENTAL CARIES

The existence of this situation induced Orland and his colleagues² to employ germ-free animals in the study of dental caries. This group showed that germ-free rats did not develop dental caries even when maintained on a diet that was caries-conductive in conventional animals. Subsequently they reported³ that caries could be induced in otherwise germ-free rats that had been deliberately inoculated with a specific strain of enterococcus derived from a caries lesion in a conventional rat. When germ-free rats were infected with this enterococcus, plus a highly proteolytic gram-negative bacterium, there was apparently no increase in the severity of caries found. Subsequently, at the National Institute of Dental Research,⁴ a microaerophilic streptococcus was found that could induce caries in germ-free rats of the same Lobund strain as that used by Orland but maintained on a different cariogenic diet. The uninoculated germ-free control animals again showed no evidence of caries. In an extension of these studies, we have now tested⁵ a pigmented heterofermentative lactobacillus, *Lactobacillus fermenti*,⁶ a homofermentative *L. acidophilus*,⁶ a *Streptococcus lactis*, and a proteolytic *S. faecalis* var. *zymogenes*, all of rat origin, as mono-infections in germ-free animals, and have found them unable to induce caries, even though the animals were maintained on a cariogenic diet.

The significance of these findings is several fold. In the first place, it is now certain that caries will not occur in the complete absence of microorganisms, even in a susceptible strain of rats maintained on a cariogenic diet. Second, caries can occur in rats that harbor only a single type of streptococcus. Third, the organisms that so far are known to produce caries in the gnotobiotic animal need not be proteolytic. The active strain of enterococcus used by Orland and coworkers³ was described as closely resembling *S. faecalis* and distinguished by them from the proteolytic enterococcus, *S. liquefaciens* (*S. faecalis* var. *liquefaciens*), which produced "somewhat atypical carieslike lesions." The active streptococcus used by Fitzgerald, Jordan, and Stanley⁴ was also not proteolytic according to the usual bacteriological tests, suggesting that the elaboration of extracellular proteases was not an essential factor in the production of the disease.

² Orland, F. J., Blayney, J. R., Harrison, R. W., Reyniers, J. A., Trexler, P. C., Wagner, M., Gordon, H. A., and Luckey, T. D. Use of the Germfree Animal Technic in the Study of Experimental Dental Caries, *J. Dent. Res.*, 33:147, 1954.

³ Orland, F. J., Blayney, J. R., Harrison, R. W., Reyniers, J. A., Trexler, P. C., Ervin, R. F., Gordon, H. A., and Wagner, M. Experimental Caries in Germfree Rats Inoculated with Enterococci *J. Amer. Dent. Ass.*, 50:259, 1955.

⁴ Fitzgerald, R. J., Jordan, H. V., and Stanley, H. R. Experimental Caries and Gingival Pathologic Changes in the Gnotobiotic Rat. *J. Dent. Res.*, 39:923, 1960.

⁵ Fitzgerald, R. J., and Jordan, H. V. Unpublished results.

⁶ Jordan, H. V., Fitzgerald, R. J., and Faber, J. E. A Survey of Lactobacilli Including Pigmented Strains From the Oral Cavity of the White Rat, *J. Dent. Res.*, 38:611, 1959.

The caries-active streptococci are strongly acidogenic and produce lactic acid almost exclusively when fermenting sugars in vitro. However, special note should be given to the fact that production of acid per se is not the sole determinant of cariogenicity in microorganisms. It has already been mentioned that other equally acidogenic streptococci or lactobacilli were unable to induce caries in gnotobiotic rats.

This concept has received additional support from the parallel studies of Keyes⁷ on caries in a strain of albino hamsters. Keyes found that successive generations of one subline of hamsters, originally derived from a caries-active female that had been treated with penicillin, remained caries-free even when maintained on a diet that was normally associated with the rapid and rampant development of caries. He showed that this was presumably due to the fact that these animals no longer harbored a cariogenic microflora because, when simply placed in contact with caries-active animals, they readily developed the disease. According to our definition of the term, these hamsters, which lack a cariogenic microflora, can also be considered as gnotobiotic animals.

Fitzgerald and Keyes,⁸ following up these observations, were able to isolate from a carious lesion in a hamster a number of closely related strains of a streptococcus that would produce typical lesions of caries when inoculated into the oral cavity of the "caries-inactive" subline of albino hamsters. A variety of other microorganisms isolated from caries-active or the caries-inactive hamsters were unable to induce caries development when tested under the same conditions. Among the organisms tested and found inactive were various lactobacilli, streptococci, diphtheroids, and yeasts.

In addition, the streptococcus found by Fitzgerald, Jordan, and Stanley⁴ to be cariogenic in gnotobiotic rats was without effect in the hamster. Conversely, the hamster-cariogenic streptococcus was ineffective in gnotobiotic rats.

It should be emphasized that dental caries as a disease is a highly complex process, dependent on the interaction between a cariogenic diet, a susceptible host, and a suitable microflora. Elimination of any one of these factors will prevent development of the disease. Considered primarily from the microbiologic standpoint, however, it begins to be evident that caries in experimental animals has many of the attributes of a specific bacterial disease, in which the primary etiologic agent may be a single type or a relatively few types of microorganisms specific for each species of animal. While it would be premature to suggest that a similar situation exists in the case of caries in humans, the implications of these findings in laboratory animals certainly cannot be ignored in future studies on this disease in humans.

DENTAL CALCULUS

The association of micro-organisms with dental calculus in humans is too well known to require documentation. It was a matter of some surprise to us, therefore, when, in some of our early germ-free rat experiments, we noted supragingival calculus-like deposits on the maxillary molars. At about the same time, Baer and Newton⁹ reported a similar phenomenon in germ-free mice. These deposits were gritty in texture and stained readily with alizarin red S. Fitzgerald and McDaniel¹⁰ collected sufficient of this material from germ-free rats to permit X-ray diffraction studies and found that typical apatite patterns were formed. It should be noted that the extent of calculus deposition in the germ-free animal seldom approaches that seen in conventional animals on the same diet. We regard this as an indication that, in the normal non-germ-free state, micro-organisms contribute to the severity of the deposits. Nevertheless, these findings indicate that it will be necessary to look beyond the microflora in seeking to determine the etiology of calculus formation.

⁷ Keyes, P. H. The Infectious and Transmissible Nature of Experimental Dental Caries, *Arch. Oral Biol.*, 1:304, 1960.

⁸ Fitzgerald, R. J., and Keyes, P. H. Demonstration of the Etiologic Role of Streptococci in Experimental Caries in the Hamster, *J. Amer. Dent. Ass.*, 61:9, 1960.

⁹ Baer, P. N., and Newton, W. L. The Occurrence of Periodontal Disease in Germfree Mice, *J. Dent. Res.* 38:1238, 1959.

¹⁰ Fitzgerald, R. J., and McDaniel, E. G. Dental Calculus in the Germfree Rat, *Arch. Oral Biol.*, 2:239, 1960.

PERIODONTAL DISEASE

As might be anticipated, the same reasons which led to the use of gnotobiotic rats in caries research would also apply in the study of periodontal disease. Fitzgerald et al.⁴ described gingival lesions in germ-free rats caused by impaction of ingested hair. Baer and Newton⁹ reported alveolar bone resorption in germ-free mice receiving a presumably adequate diet. Thus far, there have been no studies reported in which germ-free animals have been deliberately monoinfected with specific organisms to assay the effects on the gingival tissue. However, in connection with monoinfected germ-free rats used for caries-induction experiments, we have not encountered any evidence that the organisms employed demonstrated any pathogenicity for the gingival mucosa. It is quite possible that the white rat, which has a rather high resistance to infections in general, is not the best animal to use in studying this problem. For this reason, interested investigators are looking forward to the time when more suitable animals are available in the germ-free state. These would include the hamster, the cotton rat, and the rice rat.

SUMMARY

Attempts to use germ-free animals in studies of oral diseases have thus far been limited. However, in those instances in which the gnotobiotic technique has been employed, the results have been extremely fruitful and informative. Dental caries has been induced in gnotobiotic rats with single strains of streptococci. Dental calculus has been observed to occur, in both rats and mice, in the absence of all demonstrable micro-organisms. It appears evident that the gnotobiotic technique will prove extremely useful in studies directed toward the final elucidation of the actual mechanisms by which these diseases are produced. In addition, it seems quite probable that this technique will be of material aid in the separation and study of the factors that contribute to the development of periodontal pathology.

FLUORIDATION

MR. DENTON. Now, research relating to water fluoridation.

DR. ARNOLD. We are doing very little at the present time in research directly on water fluoridation, Mr. Denton. As I reported here just a little bit ago, some of the basic laboratory research is related to this, such as the effect of fluoride on the improving of and crystallization of the dental structures and bone structures.

Our research, which is indirectly related to water fluoridation, has to do with following out and determining just where water fluoridation has its effects, and, secondly, we are doing studies on other methods of using fluoride than in the water supply, thinking particularly toward people in rural areas and so forth.

MR. DENTON. I saw in the paper that dental cavities had been reduced 50 percent in the District of Columbia because of fluoridation.

DR. ARNOLD. I saw that and was happy to see it.

DR. TERRY. Mr. Denton, a great deal of our observations in the area of fluoride are done in our Dental Public Health Division downtown, because it is more related to the applied aspect, rather than the basic research.

MR. DENTON. Some years ago we discussed the fact that many small towns did not have competent engineers or did not have engineers with sufficient training to fluoridate the water, and the program should be started to train engineers in smaller communities to work on fluoridation of water.

Has that program gone any further?

DR. ARNOLD. Again I will answer that, Mr. Denton, and refer, as Surgeon General Terry did, to the fact that most of these programs are run in the Division of Dental Public Health and Resources.

Yes, they have put in courses, I know, to train personnel through courses arranged at their State health departments, and so forth, which will train people in the smaller communities.

EPIDEMIOLOGICAL STUDIES

Mr. DENTON. Now, do you want to discuss epidemiology?

Dr. ARNOLD. Well, I can truthfully say we have plans. As you know, I reported in the past year we have had very good leads, from an epidemiological standpoint, particularly in our studies associated with the Interdepartmental Committee on Nutrition for National Defense. We have been running epidemiological studies in conjunction with a large group of people interested in nutrition in many of the more remote or less-developed countries in the world.

We have found, particularly, variations in both dental caries and in periodontal diseases. We are planning, under the 1964 budget, to go back and make a more concentrated epidemiological study in Trinidad and, I believe, Ethiopia was one of the other places where we are planning to go back. Because the original surveys were intentionally survey-type, I do not mean to say superficial, but they only gave us leads. We can go back, and from an experimental standpoint, now do a more concerted epidemiological study of the conditions.

INFECTIOUSNESS OF DENTAL CARIES

Mr. DENTON. Now, do you want to say anything in regard to research related to infectiousness of dental caries?

Dr. ARNOLD. Well, I did report on the infectiousness or transmissibility of dental caries last year. We have continued these studies.

As far as confirming them in animals are concerned, they have been well confirmed in animals. We have attempted to translate some of these findings into human beings. Since we cannot have a germ-free human being at the present time, we have two studies in operation, collaborative studies: one supported by grants, and one in full collaboration with our Institute.

One is at the National Children's Cardiac Hospital in Miami, and the other is at the Heart Haven Hospital in Lancaster, Pa., where children have been under long-term antibiotic treatment, which cuts down the number of bacteria we have to look into.

It does not by any means make them germ free; but it does eliminate certain types of their bacteria, and gives us a more narrow field to go into.

So far, these studies have not been in progress long enough to make any reports.

Mr. DENTON. Is there anything else you want to say?

Dr. ARNOLD. No, Mr. Denton. I have nothing further to submit for the record.

I do want to thank you people for the kind attention I have had here, and we appreciate how deeply you have looked into our problems.

Mr. DENTON. We thank you.

We will adjourn until 10 o'clock tomorrow.

MORTALITY, MORBIDITY, AND COST OF DENTAL ILLNESS

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the Dental Institute, and the estimated annual cost to the Nation.

1. *Deaths related to dental disease.*—No information available.

2. *Disabilities caused by dental diseases.*—Oral diseases constitute a major national health problem. Dental caries and periodontal disease are the most prevalent and important diseases, but many other conditions ranging from canker sores to oral cancer cause disabilities to varying degrees. It is ironic that teeth can be saved through preventive measures such as fluoridation, only to be lost to periodontal disease, the cause of which is still unknown. The magnitude of this problem is difficult to measure in terms of financial losses, pain and suffering involved, and the effect on the general health of the public. It is estimated that 95 percent of the population of the United States have decayed teeth—over 90 percent of school age children, 9 in every 10 adults. Periodontal disease, or pyorrhea, has attacked half of the population by age 50, and almost all by age 65, and is the primary cause of tooth loss in adults. Each year sees some 8,000 children born with cleft palate, the most common of all congenital anomalies.

3. *Estimated annual cost to the Nation.*—Americans have some 700 million untreated cavities, an average of 4 each. It has been estimated that as many as 85 million man-hours of industrial production time are lost annually due to oral diseases. The progressive, cumulative nature of oral conditions means more treatment time, placing an enormous burden on a profession already critically short of manpower. The yearly bill for dental care is about \$2 billion, but this represents treatment and care for less than half the people who need it. There is also a direct relation between oral health and many systemic conditions affecting the body as a whole. This lack of understanding or oral health increases a public health problem already complicated by a shortage of dentists and higher costs of treatment. The role of research in every aspect of this problem is evident, since research can provide a key to causes, analyses of method of treatment, and road to prevention of disease.

HIGHLIGHTS OF PROGRESS IN RESEARCH IN ORAL DISEASES 1962

Items of Interest on Program Developments and Research Studies Conducted and Supported by the National Institute of Dental Research

DENTAL CARIES

FIRST EFFORTS AT VACCINE TO PREVENT TOOTH DECAY IN EXPERIMENTAL ANIMALS

The demonstration that dental decay could be induced in a strain of caries-inactive hamsters by oral inoculation of a specific strain of streptococcus has enabled NIDR scientists, for the first time, to undertake the testing of an experimental anticaries vaccine. Initial findings were reported at the International Association for Dental Research meeting in St. Louis, Mo., by Dr. Robert J. Fitzgerald, Chief, Gnotobiotics Section, and Dr. Paul H. Keyes, Laboratory of Histology and Pathology, NIDR.

Biologic research in recent years has provided important new knowledge of the etiology and mechanism of dental decay. Following the discovery in the research laboratories at the University of Notre Dame that dental caries would not occur in germ-free rats in the absence of bacteria, scientists at the Dental Institute were successful in isolating specific decay-producing micro-organisms in the rat and the hamster using the germ-free technique. Further, it was found that the cariogenic streptococcus (strain AF-1) from rats had no effect on hamsters; and, conversely, a different streptococcal pathogen (strain HS-6) obtained from caries-active hamsters was not cariogenic for rats.

Paralleling these studies to identify the involved oral pathogen were the findings that dental decay could be transmitted from caries-active animals to caries-inactive animals, and that such transmission could be terminated with

antibiotics. On the basis of these interrelated findings, NIDR scientists have recently begun studies to determine the feasibility of vaccines for immunizing laboratory animals against tooth decay.

In the initial study using the HS-6 host-specific strain of streptococcus that induces caries in the albino hamster, the scientists injected breeding female hamsters with a preparation of killed HS-6 vaccine, either subcutaneously or intraperitoneally. All offsprings were infected orally with the pathogenic streptococci at weaning, and part of the litter was given a series of five weekly injections of the same vaccine and placed on a caries test diet for 42 to 61 days. Offspring from unvaccinated dams (females) of the same stock served as infected and uninfected controls.

Preliminary results showed that none of the infected animals achieved immunity to caries, regardless of whether or not the animals were vaccinated. The uninfected controls showed negligible caries activity. Similarly, no protection against caries was shown in hamsters given triweekly injections for 3 weeks of a rabbit serum containing antibodies against the HS-6 streptococci.

These negative results of attempts to immunize hamsters with the cariogenic streptococcus are consistent with other observations in humans and animals that one episode of caries does not confer immunity against succeeding attacks. This in turn suggests that even if it is possible to determine the cause of caries in humans, measures other than immunologic may have to be sought to control the disease.

TOOTH DECAY SEEN RELATED TO FREQUENCY OF EATING RATHER THAN AMOUNT EATEN

Study by NIDR scientists shows that reduction of food intake confirms a suspected association with reduced caries activity in controlled feeding. Rats fed a caries test diet for one-third of a day developed relatively little caries activity, whereas rats with food available 24 hours a day showed significantly more caries activity.

This study was made by Dr. Rachel H. Larson, Gnotobiotics Section, Laboratory of Microbiology, Dr. I. Zipkin, Laboratory of Biochemistry, NIDR, and Dr. M. Rubin, Georgetown University, Washington, D.C. Their findings are reported in "Archives of Oral Biology."

Since caries is related to the interaction between dietary substrate, decay-producing bacteria, and host susceptibility, modification of any of these factors may alter the activity of the disease. In addition to the role of dietary carbohydrates, the physical nature of a diet, and its water and fat content in the development of dental caries, the frequency of feeding and amount of food consumed have long been suspected as influencing factors. This study sought to evaluate the relationship of diet to dental caries under experimental conditions of controlled feeding.

Ethylene diamine tetraacetic acid (EDTA), a chelating agent, was administered by injection to another series of animals, producing lethargy and anorexia. These changes in the biologic status affected the host-diet-microflora relationship. The EDTA-injected animals consumed less food than untreated controls fed for the same length of time but showed more caries activity, due at least in part to the toxicity of the compound.

Animals on each of three test diets showed caries activity to be directly related to the length of time that food was available and not to the amount of food consumed. The findings suggest that increased oral retention, whether resulting from changes in the feeding regimen or changes in the biologic status of the animal, may be a common causative factor associated with increased caries activity.

DECAY-REDUCING EFFECT OF FLUORIDATED WATER LASTS INTO ADULT LIFE

NIDR grantees reported on the first study conducted in the United States in which the dental caries experience of adult natives of a city with an optimum concentration of naturally fluoridated water (Aurora, Ill., 1.2 p.p.m.) was compared with that of adult native residents of a nearby fluoride-deficit city (Rockford, Ill., 0.1 p.p.m.). Other U.S. studies have reported on persons using either heterogeneous or higher levels of fluoride in communal water supplies.

The 2-year study was conducted by Harold R. Englander, D.D.S., and Donald A. Wallace, Ph. D., at the College of Dentistry, University of Illinois. Dr. Eng-

lander is now a member of the Epidemiology and Biometry Branch, NIDR. The report appears in Public Health Reports.

The investigators examined 896 residents of Aurora, and for comparison, 935 natives of Rockford. Volunteer groups in both cities were about equally divided with respect to sex, age (18-59 years, with mean of 33.6 and 33.1, respectively), and were comparable with respect to socio-economic status, education, and dietary habits.

Results showed that there was a significantly lower incidence of dental caries in Aurora than in Rockford. Aurora subjects had an average of 10 DMF teeth (decayed, missing, or filled) and 22 DMF surfaces, while their Rockford counterparts had 17 DMF teeth and 43 DMF surfaces. Thus, the dental caries experience of Aurorans was roughly 40 to 50 percent less when evaluated by teeth and surfaces. These findings support evidence found in earlier studies that the caries inhibitory effect of fluoride in children who consume fluoridated water is maintained into adult life.

FLUORIDE STUDIES

FLUORIDE MAY PROTECT TEETH BY INCREASING PHYSICAL AND CHEMICAL STABILITY OF BONE

Results of an X-ray diffraction study by NIDR scientists using powdered human bones have revealed changes in the size and perfection of the bone crystal which may help explain certain physical and chemical properties peculiar to bones and teeth containing fluoride. The findings may also shed light on the reason enamel of fluoride-protected teeth is more resistant to decay.

Studies in this continuing research were made by Drs. I. Zipkin, Laboratory of Biochemistry, and A. S. Posner and E. D. Eanes, Laboratory of Histology and Pathology, NIDR. Their findings are reported in *Biochimica et Biophysica Acta*.

The investigators used iliac crests, ribs, and vertebrae obtained at post mortem from 20 individuals in four areas where municipal water supplies contained fluoride ranging from 0.1 to 4.0 parts per million. Ages of individuals ranged from 56 to 83 and their residence in the four areas was from 21 to 38 years.

Findings revealed that human bones with relatively high fluoride content tended toward crystal perfection, thus increasing the physical and chemical stability of these bones. Also, fluoride replaced the hydroxyl ions in the calcium phosphate of bone, thus making the bones less soluble. Both effects would be expected to produce a more stable bone, physically and chemically. These observations may help explain why the ingestion of additional fluoride, in certain diseases such as osteoporosis, tends to reduce the loss of bone calcium.

Since bones and teeth share some common properties, this research may have important relevance to caries etiology. If these findings can be related to enamel, they may help explain the caries-inhibiting properties of fluoride in teeth.

MOTTILING OF TEETH FOUND LOW IN GRAND RAPIDS AFTER 17 YEARS OF FLUORIDATION

The final field examination in a 17-year study of the effects of fluoridation of community waters was carried out in Grand Rapids, Mich., during the fall of 1961. In this survey, 822 students, aged 12-14 years, who had used fluoridated water since birth, were examined for signs of fluorosis. Slightly over half of the children fulfilled the requirement of having spent their first 7 years in the city. This period was specified since calcification of enamel of all of the permanent teeth except the third molars is completed during this span, and enamel once calcified can no longer become fluorosed.

This pioneer project has been a collaboration between the Epidemiology and Biometry Branch, NIDR, the University of Michigan, Michigan State Department of Health, and the city-county health department of Kent County, Mich.

The study, by Dr. A. L. Russell, Chief, Epidemiology and Biometry Branch, NIDR, is reported in the *Journal of the American Dental Association*.

The findings provide definitive evidence that, at the optimum level of 1.0 p.p.m. fluoride in the community water, there is a decided margin of safety against

mottling. When the Grand Rapids children were compared with similar age Maryland residents exposed since birth to low levels of fluoride (0 to 0.2 p.p.m.), no greater prevalence of enamel opacities was noted. It was also observed that the prevalence of fluorosis was considerably lower than initially predicted, on the basis of findings in communities with natural fluoride waters with a comparable average concentration. This may be due to the rigid control of the ion in fluoridated systems in contrast to the fluctuant levels in natural systems.

An additional finding of interest was that enamel opacities were only slightly more numerous in children with maximum exposure to the Grand Rapids community water during the calcification period than in children who had undergone less exposure to fluoride, i.e., those with considerable periods of residence away from the fluoridated community.

STANNOUS FLUORIDE BETTER THAN SODIUM FLUORIDE IN REDUCTION OF TOOTH DECAY

A grantee of the National Institute of Dental Research has found that frequent application of low concentrations of sodium or stannous fluoride is effective in preventing acid penetration of tooth enamel, and that stannous fluoride provides greater protection than sodium fluoride.

Local application of sodium fluoride is known to make tooth enamel more resistant to decay. Investigators have been studying numerous other fluoride salts to discover how to best utilize the protective qualities offered by these chemical compounds.

The purpose of this investigation by E. E. Fischer of Tufts University School of Dental Medicine, reported in the *Journal of Dental Research*, was to compare the relative effectiveness of sodium fluoride and stannous fluoride in reducing incidence of dental caries when applied frequently at the low concentrations of fluoride-containing dentifrices. The author also wanted to observe whether the effectiveness of such fluoride treatments in adults diminished proportionately with the age of the tooth.

Freshly extracted central incisors were grouped according to the age of the patients: (1) 20-34 years; (2) 34-50 years; (3) over 50 years. Each tooth was cut into six sections and each section was imbedded between glass slides in an epoxy resin with its labial (lip) enamel exposed by a slot in the slide. The slides were then immersed in a sodium lactate buffer of pH 5.0 and randomly selected for three different treatments: (1) 0.027 solution of sodium fluoride; (2) 0.05 solution of stannous fluoride; (3) demineralized water (controls). For some slides, applications occurred twice a day; for others, once a day. This is comparable to the frequency and concentration of fluoride application in dentifrices. Periodic measurements of acid penetration into the tooth enamel of each section were made.

It was found that all sections treated with a fluoride solution showed less total penetration by acid than those treated with water. Sections treated only once a day with stannous fluoride had a rate of penetration similar to those treated twice a day with sodium fluoride. Sections treated twice a day with stannous fluoride experienced the least amount of decalcification of all the experimental sections. The investigator found indications that the protective action of fluoride occurred at the interface of sound and demineralized enamel. The age of the tooth did not alter the effect of either fluoride solution.

GROWTH AND DEVELOPMENT

THALIDOMIDE ADMINISTERED TO PREGNANT RATS PRODUCES MALFORMATIONS IN PROGENY

Various investigators who have studied the teratogenic effects of thalidomide in the rat have reported resorptions of fetuses but generally no malformation. Other studies of thalidomide absorption in the rat have shown that peak blood levels occurred after 15 minutes of oral administration of the drug and peak concentrations in the brain within 30 minutes after administration, demonstrating that rapid absorption from the gastrointestinal tract took place.

In the light of these reports, Drs. C. T. G. King, Laboratory of Biochemistry, and F. J. Kendrick, an American Dental Association research associate, NIDR,

conducted a study of the possible teratogenicity of the drug when administered at different times of gestation (8 to 17 days) in the Sprague-Dawley rat. Their report appears in *Lancet*.

One day before expected spontaneous term delivery (20th day), the pregnant rats were sacrificed and their young examined for gross malformations. Once these were recorded, the young were fixed in 80 percent alcohol, cleared with one percent KOH, the skeletons selectively stained with 0.05 percent Alizarin red S., and observed for skeletal malformations.

Examinations of 520 fetuses from 55 pregnant rats showed 36 gross malformations, ranging from malrotation of the hind limbs to hamartoma of the palate, with accessory incisors, extremely small fetuses, and absence of tail. The technique of clearing the fetuses demonstrated 40 more anomalies, the most common being the appearance of a subcutaneous, cartilaginous-like mass of tissue from the mid-dorsum to the tail of the fetus.

In the course of research on prenatal influences on oral-facial development and dental caries susceptibility of progeny, Drs. King and Kendrick examined over 10,000 rat fetuses of the Sprague-Dawley strain during the past 2½ years, without finding any type of malformation in control animals.

Drs. King and Kendrick are continuing their studies with thalidomide to learn exactly how malformations are formed at different stages of gestation and in different species of animals.

HEREDITARY FACTORS NOTED IN THE DEVELOPMENT RATE OF THE TEETH AND BONES

Similarities between sisters reflect genetically determined aspects of developmental timing relating to X-chromosome inheritance.

In accordance with genetic theory, one would expect full sisters, who share the paternal X-chromosome in common, to be more similar in certain characteristics than full brothers or siblings of opposite sex. Identical twins, who also share common chromosomes, have shown a high correlation in bone ossification rate, ossification timing, and calcification timing of the posterior permanent teeth.

S. M. Garn and C. G. Rohman of the Fels Research Institute, Yellow Springs, Ohio, reviewed sibling comparisons involving 318 sister-sister, brother-sister, and brother-brother pairs, and found a tendency for greater similarity in developmental timing in sister-sister pairs. These similarities were manifested in the ossification rate, ossification timing and calcification timing of the posterior permanent teeth, all of which appear to be gene-determined.

The number of ossification centers of the hand present at half-year intervals from 1 to 7 years, and the age at appearance of 28 individual ossification centers of the hand proved more alike in full sisters than in the other pairings considered. Similarly, the age at appearance of specific stages of calcification of five mandibular posterior teeth was more alike in sister-sister pairs.

Since the sample size of the investigation was large and serial longitudinal observations were involved, the investigators feel the findings are statistically significant, and that the shared X-chromosome is a determining factor in bone development and tooth calcification. These studies support previous investigations which also give evidence of sex-chromosome influence on developmental timing. Thus, it has been noted that in all developmental events, even those which precede steroid-hormone differentiation, girls are ahead of boys.

Additional evidence of X-chromosome influence on hand-wrist ossification and dental calcification could come from the comparison of parents and their children at identical ages. Here, the greatest degree of similarity might be expected for father-daughter pairings. The investigators are making such a survey, but at present have too small a sample of two-generation studies to warrant a judgment.

This research was supported in part by grants from NIDR and NIAID and is reported in *Nature*.

CHROMOSOMAL ANOMALIES DISCOVERED IN FEMALES, WITH "O-F-D SYNDROME"

A recent study has revealed a chromosomal aberration in patients with a little understood syndrome involving congenital abnormalities of the oral, facial, and

digital structures, sometimes seen in patients with cleft palate and/or lip. The syndrome appears to affect only females, and a familial background has been demonstrated in some cases.

The oral-facial-digital (OFD) syndrome includes malformation of the oral cavity involving the palate, tongue, alveolar processes, and the mucous membranes of the cheeks and gums. Facial structures variably involve the orbits, nose, lip, and mandible. Minor deformities of the hands and feet are frequently noted. Central nervous system defects with mental retardation are found in a significant number of these patients.

This study by A. L. Ruess, Ph. D., and his associates at the University of Illinois, carried out under a grant from NIDR, involved 12 patients exhibiting this syndrome. For each patient, somatic, radiographic, developmental and genetic, and familial analyses were performed in an effort to determine the background of the condition.

Two of the OFD patients in this study, a mother and daughter, were shown to have an insertion in one No. 1 chromosome. It appears likely that the syndrome generally is caused by partial tripling of a specific chromosome segment.

On the basis of this and previous studies, it is reported that from one-third to one-half the patients with OFD syndrome are mentally retarded. Radiographic and cephalometric studies show specific changes in the skull and digital bones. Baldness, coarse skin, and abnormal width between the eyes have also been noted.

This research was reported in Pediatrics.

HEARING LOSS IN CHILDREN WITH CLEFT LIP AND PALATE GREATER UNDER AGE SIX

Audiometric studies by an NIDR grantee have revealed that there are significant differences in hearing difficulties among children with cleft palates and that these difficulties vary as a function of age. The incidence of hearing loss and the magnitude of threshold deviations were significantly greater in the younger age groups.

It has been well established that the incidence of hearing loss in children with cleft palates is greater than that to be found in similar populations of children without clefts. Until recently it was assumed that hearing losses among children with cleft palates were homogeneous, and were due to damage of the eustachian tube apparatus and its extrinsic musculature.

Dr. D. C. Spriesterbach and his associates at the University of Iowa, working under grants from NIDR and NIMH, studied 100 boys and 63 girls of differing ages with varying types of lip and palate clefts. Each patient was given bilateral, pure-tone, air-conduction threshold tests at frequencies ranging from 250 to 8,000 cycles per second. The resulting data were evaluated according to definition of hearing loss, sex, type of deformity, type of repair, age of repair, oral breath pressure ratios, and presence or absence of congenital anomalies other than the cleft.

Among the more significant findings were:

(1) Children who were 6 years of age or older when they were tested had a significantly smaller incidence and magnitude of hearing loss than did children tested before 6 years of age.

(2) Subjects with cleft palate and associated anomalies were found to have a significantly greater incidence of hearing loss and larger threshold deviations than those with the same type of cleft without associated anomalies. Curiously, however, no significant difference was found between the groups with combined cleft lip and palate who had associated anomalies, and those who did not.

(3) Although it had been thought previously that treatment of clefts by a prosthetic appliance resulted in greater hearing loss than did treatment by surgery, the present study showed no such relationship.

This study points out some variables which may be useful in understanding and explaining the incidence of hearing loss in children with cleft palate.

This research was reported in Plastic and Reconstructive Surgery.

GROWTH OF SOFT PALATE COMPARED IN CHILDREN WITH AND WITHOUT CLEFTS

Growth of the soft palate is apparent from birth through 7 years of age, though the length of the soft palate of children with cleft palate is consistently shorter compared to that of normal children.

At the University of Illinois Cleft Palate Clinic, Drs. Peter J. Coccaro of the NIDR Clinical Investigations Branch, J. Daniel Subtelny of the Eastman Dental Dispensary, Rochester, N.Y., and Samuel Pruzansky of the University of Illinois, studied 57 cleft palate children from birth to age 7 and compared them with two control groups, in an effort to answer two questions: (1) Is the soft palate of newborns shorter when the palate is cleft? (2) How does the growth of the cleft soft palate compare with that of the normal? The results of their study are reported in Plastic and Reconstructive Surgery.

The most rapid growth in length was noted for birth to 2½ years of age for cleft palate subjects, while for the control groups it occurred between birth and 1½ years. The pattern of the growth curve appeared to differ between the two groups. From 3 to 5 years a period of less active growth was noted for all groups followed by a renewed growth period up to 7 years of age.

The cleft lip and alveolar process group and the normal group were essentially comparable when incremental changes in the length of the soft palate were evaluated.

Average measurements of soft palate length showed that the cleft palate group at the earliest age level and consistently thereafter showed shorter soft palate length than the normal and cleft lip only (control) groups.

The authors believe that the shorter soft palate in cleft palate individuals may be the result of atrophy due to improper function during prenatal development. They also conclude that, since the soft palate continues to grow, there is no functional atrophy secondary to the defect. Deficiency or displacement of the bony and/or soft tissue structures involved in the anatomic defect seems to be a more feasible factor for the short velar length at birth.

PERIODONTAL DISEASE

DENTAL AND PERIODONTAL DISEASES STUDIED IN VARIOUS GEOGRAPHIC AREAS

Surveys to identify patterns of association between nutrition and oral disease in selected populations continued to provide important information on disease prevalence and severity in various ethnic groups.

Investigators from the Epidemiology and Biometry Branch, NIDR, under the direction of Albert Russell, Chief of the Branch, in collaboration with the Interdepartmental Committee on Nutrition for National Defense, reported on studies in Vietnam, Lebanon, and Burma. In the 3 years of Institute participation in these surveys, field examinations have been completed in 14 countries including such diverse areas as Africa, North and South America, southeast Asia, and the Middle East. Employing a team approach, dental epidemiologists work closely with specialists in nutrition, medicine, biochemistry, food technology, and agriculture.

Findings from the latest studies corroborate earlier evidence that the prevalence of dental caries varies widely in different geographic areas. High prevalence levels, similar to those reported for the continental United States, were seen in the larger villages of Alaska, throughout Trinidad, and in most areas surveyed in South America. Conversely, a very low caries rate was observed in Ethiopia, where an average of less than one decayed tooth per person was seen at all ages up through 40 years. Dental caries was almost as rare in Eskimos of remote Alaskan villages, in South Vietnam, Palestinian refugees in Lebanon and in Burma. Preliminary analyses of data have shown no consistent relationship between dietary or nutritional findings and dental caries except a general tendency toward low caries prevalence in areas where caloric intake was marginal or where the use of refined carbohydrate was limited.

On the whole, periodontal disease constituted a much greater problem than caries in most of these national groups. Disease levels lower than those observed in the United States were seen only in remote areas of Alaska and in the Jivaros of Ecuador. Gingival disease with relatively little tooth loss from this cause

was reported from Ethiopia. Elsewhere the onset of periodontal disease was early, prevalence was virtually universal even in young individuals, and severity was extreme.

Despite their favorable experience with dental caries, as many Lebanese as U.S. citizens were toothless in middle life due to loss of teeth from destruction of supportive tissues. Equally high levels of disease were seen in Trinidad and the three countries of southeast Asia—Vietnam, Thailand, and Burma. The collective data have so far produced no consistent patterns of association between nutrition and periodontal disease.

ORAL ABNORMALITIES FOUND IN HAMSTERS FOLLOWING INOCULATION OF RAT VIRUS

A cooperative study between NIDR and Dartmouth Medical School scientists described the development of periodontal lesions and other dental abnormalities in Syrian hamsters following inoculation of a rat virus during the first week of life. These abnormalities are similar to those seen in the human Mongoloid patient.

The study was made by Dr. Paul N. Baer, Clinical Investigations Branch, NIDR, and Dr. Lawrence Kilham, Dartmouth Medical School, and was reported in Oral Surgery, Oral Medicine, and Oral Pathology.

While the principal finding of an earlier study by Kilham was the demonstration of a relationship of the rat virus to a syndrome of abnormalities in hamsters that resembled Mongolism in man, the suggestive clinical evidence reported by an NIDR grantee (M. M. Cohen, et al.) in 1961 that periodontal disease is prevalent in the Mongoloid child justified this further experimental investigation.

The study by Baer and Kilham demonstrated that in addition to severe alveolar bone loss and periodontal tissue destruction in hamsters infected with rat virus, there also occurred a striking abnormality of tooth development characterized principally by small crowns and roots (microdontia) and frequent supernumerary formations. These findings emphasize the importance of further clinical studies to clarify the etiologic relationship of Mongolism in man to oral-dental abnormalities.

CARTILAGE IMPLANTS AID BONE REGENERATION IN PERIODONTAL DISEASE

Studies by NIDR grantees have indicated that cartilage fixed in alcohol and preserved for several weeks is effective in the stimulation of bone regeneration in periodontal disease.

Cartilage has been used in reconstructive surgery for over half a century, but only recently have cartilage grafts been used in dentistry to stimulate production of new bone.

In former experiments, cartilage was found to act as scaffolding around which new bone could grow. In some cases, new bone fills in areas of resorption as cartilage transplants become resorbed. Fixing cartilage with alcohol before implanting appears to increase the rate of resorption, and hence the possibility of bone regeneration. If fresh, live cartilage is used, it becomes surrounded by a fibrous connective tissue sheath and remains dormant in the host, undergoing little if any resorption. So far, the outcome of any cartilage graft remains unpredictable.

E. M. Schaffer and M. W. Packer of the University of Minnesota, NIDR grantees, have studied the implantation of cartilage grafts under experimental conditions. Periodontal pockets were surgically prepared in the mouths of eight dogs. Cartilage for grafting was obtained from the dogs' ears and prepared as follows: (1) Fresh cartilage; (2) cartilage fixed in alcohol and refrigerated for 7 days before grafting; (3) and cartilage fixed in alcohol and refrigerated 40 days before grafting. The three types of cartilage grafts were placed in alternating periodontal pockets along with ungrafted pockets which served as controls.

When the grafts were examined 90 days later, it was found that the fresh cartilage had begun to degenerate. In the 7-day preserved grafts, new bone was present around the grafts, but there was no bony invasion. In the 40-day preserved grafts new bone apposition was seen directly on the surface. The authors believe alcohol fixation of cartilage enhances direct bone apposition. Changes in the matrices of all the preserved cartilage, as indicated by shrinkage of

cellular elements and degeneration of nuclei, were more pronounced than in the dormant fresh grafts. Killing the cartilage cells before grafting, therefore, appears to encourage bone formation rather than inhibit it.

The investigators also noted that if the natural fibrous membrane (perichondrium) was not completely removed from the cartilage before grafting, no apposition of new bone and cartilage occurred.

Some new bone was formed in the control pockets. This was attributed to the fact that the pockets were surgical rather than pathologic. Cementum and dentine chips from notching the teeth apparently stimulated bone formation in all the wounds.

This research was supported by NIDR and reported in Dental Progress.

MICROBIOLOGY

ELECTRON MICROSCOPE SHOWS POSSIBLE MODE OF BACTERIAL CONJUGATION

A study by an NIDR scientist of the extremely rare phenomenon of conjugation in bacteria revealed a type of ultrastructure not previously reported. There is speculation that these unusual structures may be conjugatory bridges.

This study, by Dr. Howard A. Bladen, Jr., Laboratory of Histology and Pathology, NIDR, was reported in the Journal of Bacteriology.

Various investigators have repeatedly sought evidence for sexual reproduction of bacteria, both by attempts to cross particular strains and by observation of stained preparations and electron micrographs. The discovery, in 1946, of genetic recombination of one strain of bacteria (*Escherichia coli* K-12) was shown later to be a true sexual process requiring live, intact cells as well as actual cellular contact. The phenomenon is somewhat analogous to fertilization among higher organisms in that a transfer of genetic material takes place. The event seldom occurs more frequently than 1 per 100,000 parental cells.

In a study of the ultrastructure of a strain of *Bacteroides*, Dr. Bladen observed certain morphological entities in thin sections which he speculates may be conjugatory bridges. He reported cells which were united not by simple fusion of the cell walls, but rather by tubes or bridges of variable lengths, which occurred at different areas of the organism. The diameter of different bridges varied from 110 to 500 angstroms, and in their lengths from 0.15 to 0.9 microns. A significant observation was that the longest bridge seen was also the thickest, suggesting that increased lengths are not attributable to stretching. In addition, the cell wall of the organism appeared continuous with that of the connecting bridge. In some electron micrographs, the bridges appeared to be bordered by two double structures, each approximately the same diameter and having the same architectural pattern as the cell wall of the organism. The cytoplasmic membrane, on the other hand, appeared unbroken at the site of bridge attachment and thus would seemingly act as a barrier to DNA transfer. It is possible, however, the author speculates, that a point of discontinuity may be present in adjacent but unobserved areas, or perhaps discontinuity of the cytoplasmic membrane is not a necessary precursor for transfer of nuclear material.

Further work is now in progress to clarify the occurrence of recombination with this bacteria, the direct morphological evidence of DNA transfer, and the mode of formation and complete parts of the bridge.

ORAL BACTERIA SHOWN TO SERVE AS BASE IN DENTAL DEPOSIT MINERALIZATION

Studies by NIDR scientists have shown that oral bacteria of several types may serve as a calcifiable matrix. Although the role of salivary constituents in the formation of dental calculus has been given strong emphasis in the past, the findings suggest that the role of bacteria in the development and retention of calcified deposits is highly important.

These studies were conducted by Dr. A. A. Rizzo, Laboratory of Microbiology, and Dr. D. B. Scott, Chief, and Dr. H. Bladen, Laboratory of Histology and Pathology, NIDR. Their findings were reported by Dr. Rizzo at the New York Academy of Science Conference on Comparative Biology of Calcified Tissues.

In tests for calcifiability of bacteria, washed pure cultures of organisms isolated from calcifying human dental plaques were enclosed in sealed dialysis bags and implanted in the peritoneal cavities of rats. Nonviable organisms

were prepared in the same manner. In studies on adherence, viable organisms and teeth also were implanted together in dialysis bags. The main advantage of this system of studying calcification is that the test material remains isolated from host substances which might also calcify. At the same time, the specimen is exposed to a fluid containing soluble mineral under physiological conditions.

Following sacrifice of the animals at varying intervals, the contents of the bags were subjected to bacteriological procedures, X-ray diffraction, electron microscopy, and electron diffraction.

Electron microscopic studies showed that the bacterial cell body itself served as a focus for beginning crystallization. In some species the calcification seemed to begin within the cytoplasm of the organism in a true intracellular manner, whereas in other organisms mineralization began at the surface of bacteria.

Preliminary findings on the attachment of calcified deposits to the teeth showed grossly visible hard deposits resembling clinical calculus attached to teeth implanted with *Actinomyces israelii* for several months, whereas no attachment of deposits occurred on teeth implanted with an oral diphtheroid for 6 months.

These findings support the contention that bacteria play a significant role in the mineralization of dental deposits. Continuing studies will utilize the technique of intraperitoneal transplants to test additional organisms, bacterial products, salivary constituents and other substances for calcifiability and their influence on adherence.

RESEARCH TECHNIQUES

DIRECT MEASURE OF X-RAY FILM MORE ACCURATE THAN FIXED-POINT CALCULATION

NIDR grantees in Copenhagen recommend that radiographic measurements for correlation analysis should be directly measured and not calculated, and should be measured without using fixed marks on the film.

In research involving anthropometry where bone measurements are necessary, many studies consist of correlations between various bones or the arrangements of bones in relation to one another. Frequently these measurements can be made only by taking X-ray pictures and then measuring the internal arrangements as seen on the radiograph. It is important to assess sources of error when the value of the research depends upon the accuracy of the measurements. This is especially true when an investigator is trying to find the percentage of correlation in statistical studies.

A common procedure has been for the investigator to make pinholes or pencil point marks at critical points on his film and then to derive the measurements from these fixed points. Arne Björk and Beni Solow of the Royal Dental College, Copenhagen, Denmark, NIDR grantees, questioned whether this procedure might not introduce errors of its own, affecting correlation coefficients.

Using a series of 101 unburied skulls from India, the investigators made a series of measurements from radiographs of these skulls in which fixed points were not marked. They compared these measurements statistically with a second set from the same films after the fixed points were marked. Their findings indicate that marking the photograph introduces a systematic error which increases the coefficient of correlation. Therefore, they recommend a method using ruled cellophane sheets to determine angles and points for measurements.

The studies of indirect measurements based upon additions or subtractions from the original measurements made on X-ray film showed that correlation coefficients were significantly affected. On the other hand, correlations of independent measurements were generally reliable. Therefore, the investigators further recommend that all measurements intended for correlation analysis should be directly measured and not derived by calculation.

This research is supported by the National Institute of Dental Research and is published in the *Journal of Dental Research*.

WORKSHOP STUDIES ADHESIVE RESTORATIVE DENTAL MATERIALS

The proceedings of a workshop held at Indiana University in September 1961, sponsored by the dental study section, National Institutes of Health, and supported by a grant from NIDR, have been published in a 216-page volume, *Adhesive Restorative Dental Materials*. Included are studies and analyses of tooth structure, involving crystallography, microstructure and chemistry. The mechanisms of adsorption and adhesion as they occur in the aqueous environment of the mouth are discussed, and materials and methods of dental research are evaluated with an emphasis on those materials suitable for adhesion to tooth structure. The book was compiled and edited by R. W. Phillips of the Indiana University School of Dentistry.

ARTHRITIS AND METABOLIC DISEASE ACTIVITIES

THURSDAY, MARCH 14, 1963.

WITNESSES

DR. G. DONALD WHEDON, DIRECTOR, NATIONAL INSTITUTE OF
ARTHRITIS AND METABOLIC DISEASESDR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF
HEALTHW. G. BAYLIS, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF
ARTHRITIS AND METABOLIC DISEASESB. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL
INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	3, 838	4, 352	4, 626
Positions other than permanent.....	142	145	108
Other personnel compensation.....	56	61	84
Total personnel compensation.....	4, 036	4, 558	4, 818
12 Personnel benefits.....	447	484	533
21 Travel and transportation of persons.....	299	361	331
22 Transportation of things.....	55	71	64
23 Rent, communications, and utilities.....	81	73	77
24 Printing and reproduction.....	16	47	87
25 Other services.....	599	835	755
Payment to National Institutes of Health management fund.....	4, 487	5, 130	5, 395
26 Supplies and materials.....	774	877	885
31 Equipment.....	723	847	838
41 Grants, subsidies, and contributions.....	67, 031	87, 533	100, 952
Subtotal.....	78, 548	100, 816	114, 735
Deduct quarters and subsistence charges.....	18	18	18
Total obligations.....	78, 530	100, 798	114, 717

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	591	653	655
Full-time equivalent of other positions.....	21	19	15
Average number of all employees.....	529	565	580
Number of employees at end of year.....	579	583	588
Average GS grade.....	8.2	8.4	8.4
Average GS salary.....	\$6, 985	\$7, 629	\$7, 642

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	55,466	70,822	82,513
(b) Fellowships.....	1,748	3,927	4,019
(c) Training.....	9,818	12,784	14,420
Total, grants.....	67,032	87,533	100,952
2. Direct operations:			
(a) Research.....	9,564	10,690	11,307
(b) Collaborative studies.....	641	900	713
(c) Review and approval of grants.....	1,008	1,305	1,469
(d) Program direction.....	261	370	276
Total, direct operations.....	11,474	13,265	13,765
Total program costs, funded ¹	78,506	100,798	114,717
Change in selected resources ²	24		
Total obligations.....	78,530	100,798	114,717
Financing:			
Comparative transfers to other accounts.....	397	490	
Unobligated balance lapsing.....	2,875	2,094	
New obligational authority.....	81,802	103,382	114,717
New obligational authority:			
Appropriation.....	81,831	103,388	114,717
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (-).....	-29	-6	
Appropriation (adjusted).....	81,802	103,382	114,717

¹ Includes capital outlay as follows: 1962, \$522,000; 1963, \$847,000; 1964, \$838,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$522,000 (1962 adjustments, -\$5,000); 1962, \$542,000; 1963, \$542,000; 1964, \$542,000.

PERSONAL BACKGROUND OF DIRECTOR

Mr. FOGARTY. We have before us the request for arthritis and metabolic disease activities.

Doctor, this is your first appearance before the committee, is it not?

Dr. WHEDON. That is right, sir.

Mr. FOGARTY. As we ask all those who appear for the first time, will you give us some of your background?

Dr. WHEDON. My name is G. Donald Whedon. I am a native of Geneva, N.Y., and a graduate of Hobart College. I received my M.D. degree in 1941 from the University of Rochester. I received clinical training at the Mary Imogene Bassett Hospital in Cooperstown, N.Y., at Strong Memorial Hospital, Rochester, N.Y., and at the New York Hospital, Cornell Medical Center, in New York City.

I spent 8 years at Cornell University Medical College, initially as a research fellow and then eventually as an assistant professor of medicine.

In 1950 I was certified as a specialist in internal medicine by the American Board of Internal Medicine. In 1952 I came to the National Institutes of Health as Chief of the Metabolic Diseases Branch of this Institute, with particular interest in clinical investigation of the problems related to bone metabolism, and have also had some interest in energy metabolism in human beings.

In 1956 I was appointed Assistant Director of the Institute and just this past November appointed Director.

GENERAL STATEMENT

Mr. FOGARTY. We will put your full statement in the record. You may summarize it now.

(The statement follows:)

Mr. Chairman and members of the committee; it is with special pleasure that I appear before you today to tell you about some of the important happenings in our fields of interest, those of the arthritic or rheumatic disorders, and the diseases of metabolism.

This is my first occasion to speak to you as Director of the National Institute of Arthritis and Metabolic Diseases. As you know, Dr. Floyd S. Daft, our former director, retired last May, and I consider myself fortunate to succeed a man who so ably guided the Institute's activities during the past decade.

In this year's report I am going to depart a bit from the usual practice of presenting a lengthy list of single findings uncovered within the past 12 months. Rather, I shall attempt today to provide perspective on our accomplishments by showing the progress we have made during the past several years, relating recent individual advances to the major areas of development.

Our concern, of course, is with current progress, and how rapidly it is being made. In many cases that I shall mention today the progress is quite apparent, as well as the speed with which it has been made. But I want to emphasize, also, that not all progress is immediately perceived, especially when we consider the area of basic research. Many of the fundamental facts which are being uncovered today have no immediately apparent use, but experience has shown that these same facts may form the basis for the startling new advances of tomorrow.

THE "CODE OF LIFE"—STUDIES IN BASIC RESEARCH

As you know, in addition to its studies of arthritis and metabolic diseases, our Institute invests heavily in basic research. Since it was established in 1950, incorporating many of the early and most productive laboratories in the Public Health Service, the NIAMD has placed great emphasis on fundamental research in the closely related areas of biochemistry, enzymology, nutrition, and molecular biology. It is in this last area, molecular biology, that particularly exciting developments have occurred. They relate to our understanding of heredity and more particularly to the "cracking" of the genetic code.

The genetic code work has profound implications for our attack on the inherited diseases and has recently stimulated a great deal of important basic work. For this reason I would like to describe it in some detail.

The so-called genetic code is a mechanism through which hereditary information is perpetuated from generation to generation, and which permits living matter to reproduce itself systematically. The details of this mechanism are of tremendous interest, since once understood they might be predicted and perhaps modified, ultimately for human benefit. For some years our investigators have concentrated on nucleic acids since this mechanism has been known to involve the two nucleic acids DNA and RNA (deoxyribonucleic acid and ribonucleic acid) which occur in all living cells and direct their reproduction. The precise, detailed mode of action of the nucleic acids has been largely shrouded in mystery; new, pertinent knowledge, however, is unfolding with increasing rapidity.

Within the past few years, a pioneering experiment by NIAMD scientists illuminated the way information is coded into the molecular structure of nucleic acids, how they act as physical carriers of inherited instructions, and how their information is used to direct the production of proteins in the protoplasm of newly evolving cells.

The core of the problem is how the instructions are stored within the physical structure of the DNA molecule, carried from generation to generation, transmitted by "messenger RNA" and then used to direct the making of specific protein molecules from some 20 different amino acids. The mechanisms of this information coding system thus provide the means for passing on man's inherited characteristics, and to understand them fully is one of the most important basic problems in biology.

In their initial work, the NIAMD scientists prepared a bacterial protein-synthesizing system, literally in test tubes, that could be "directed" by insertion of samples of synthetic RNA. With this system, it was possible to determine what proteins were made by the bacterial enzymes when particular RNA samples

were used, samples whose structure consisting of various combinations of chemical groups was known. In this way, the individual RNA structure with a particular chemical group combination, could be related to the protein it produced, and so appeared to act as a code. This was the first time that such direct translation (of compound structure to synthesis of specific proteins) had been possible, and it has caused a ground swell in the world of biochemistry that has yet to subside.

Since then, the code work has been greatly extended by both NIAMD scientists and grantees, and others throughout this country and abroad. Particularly noteworthy is a group at New York University, headed by Dr. Severo Ochoa, a Nobel laureate and Institute grantee, and one at Cambridge University, England. Two members of this English group, Dr. Francis H. C. Crick and Mr. Maurice Wilkins shared the 1962 Nobel Prize in medicine with Harvard University's Dr. James Watson for their monumental work on the molecular structure of DNA.

During the past year NIAMD scientists collaborated with investigators at the University of California in studies with the RNA from tobacco mosaic virus, and found that the genetic code of this viral RNA was quite similar to that of the bacterial system. Additionally, the NIAMD scientists and other investigators have found evidence of the same type of coding in a mammalian system, so that it appears that the genetic code may constitute a common "language" understood by all living things.

An interesting number of code patterns and their respective, specific functions is now known, and we are approaching the time when we may at last understand some of the basic control mechanisms in the heredity of living cells. With this may come the understanding of how these control mechanisms can be deranged, and cause such inherited diseases as diabetes and gout. Beyond the code work itself, the entire field of biochemical genetics is developing at rapid speed, and this is reflected in many of the basic studies now underway at the Institute. Many segments of NIAMD now have an interest in one or another aspect of the genetic problem.

For example, intensive studies are being made of the chemical structure and physicochemical properties of the nucleic acids. The most sophisticated methods available are being used to determine their properties in solution and in the solid state, and the enzymes which generate and degrade them are being purified and studied. In a related area, the chromosome—the smallest visible unit of genetic transmission—is receiving special scrutiny. Abnormalities in the number and shape of these chromosomes are being correlated with specific diseases. I am happy to report that one of our visiting scientists, Dr. J. H. Tjio, who has done pioneering work on human chromosomes, recently received a special award from the Joseph P. Kennedy Foundation for this work.

Dr. Tjio gained world renown in 1956 when he and a fellow cytologist, Albert Levan, reported that human cells contained only 46 chromosomes, not the 48 that were then thought to exist. This higher number had been accepted as correct in the literature since first reported in 1923. By 1956, however, newer techniques were available and with these the two scientists consistently found only 46 chromosomes. Following this, other researchers confirmed Dr. Tjio's work and by 1959 the chromosome number for man was unequivocally established as 46.

Returning for a moment to our original concern with perspective in science, I think these basic studies point up a significant fact. As medical research became more sophisticated it focused on smaller and smaller units of living systems, and today we are at the level of individual molecules within a single cell. We are now beginning to see how these molecules are built from simple starting materials, what shapes they take, and how they become organized, in conjunction with other molecules, into living systems. Their organization might be compared to that of a watch whose many parts must all be present and in their specific places before the watch will tick. Recently, we have made some giant strides toward finding out exactly what makes the human watch tick.

PROGRESS AND PLATEAUS IN ARTHRITIS RESEARCH

The field of the rheumatic diseases during the past decade has undergone a tremendous change from what it was prior to the establishment of the Institute. The discovery of the remarkable anti-inflammatory effects of the steroid hormone cortisone in 1948 marked a striking advance. Prior to the advent of cortisone, the rheumatic disease field was one of the most neglected areas in medicine and little headway was being made in either understanding or treatment of such disorders as rheumatoid arthritis, osteoarthritis, gout, and other rheumatic diseases.

It was soon found, however, that along with beneficial effects cortisone also produced many undesirable, and sometimes dangerous, side effects. Thus began the search, which has continued ever since, for similar drugs with the same beneficial effects but fewer or no undesirable side effects. The hope that such drugs might be found or synthesized in the laboratory was partially realized in 1954 when Dr. Joseph J. Bunim, clinical director of the Institute, tested clinically the first effective antirheumatic synthetic corticosteroid drugs, prednisone and prednisolone. These drugs had been synthesized by the pharmaceutical industry and given extensive clinical study at the Institute before being released. The search still goes on and newer drugs have been introduced, but none has so far proven superior in any significant way to the original prednisone and prednisolone.

Evaluation of these new drugs and methods of treatment is a continuing activity of NIAMD arthritis researchers and grantees. During the past year some progress has been made both intramurally and extramurally. In collaboration with scientists from the National Cancer Institute, our investigators have found that intermittently administered amethopterin—a potent drug useful against certain types of cancer—brought about mild to marked improvement in patients with psoriatic arthritis. Encouraging results were obtained in 15 of 18 patients with either psoriatic arthritis or coexistent psoriasis and rheumatoid arthritis. Although amethopterin (methotrexate) is well known for its long-term toxic effects and must be used with extreme caution, the study has shown that the dosage schedule and route of administration used were safe enough to warrant further investigation under strictly controlled conditions.

In other drug evaluation work, Institute grantees have completed a widespread, multiclinic study of the various types of drug therapy now being used in rheumatoid arthritis. Currently used drugs include aspirin, corticosteroids like prednisone, gold compounds and the newer antimalarial drugs. Final statistics are not yet available, but the study indicates that the multiclinic study technique involving close cooperation among a dozen university-connected rheumatic disease centers throughout the country will produce reliable results.

There is no doubt that the drugs now being used are highly potent and irreplaceable when used in many patients, but it is also obvious that they are far from the final answer to the problem of arthritis. Conservative management of arthritis patients, without resort to these potent drugs and their attendant risks, appears to be on the increase. Most of the recent advances in the treatment of rheumatoid arthritis have been in the field of prevention of pain and deformity by careful selection of specific programs of physical medicine and by careful supervision of the patient given a minimum of potentially hazardous drug therapy.

Equally as important as the advances in treatment that have occurred during the past decade is the amassing of knowledge about the basic causes of rheumatoid arthritis and the exact mechanisms which lead to the disease processes. During the past 5 years Institute scientists and grantees have made major advances in the understanding of the so-called "rheumatoid factors" found in the blood of many patients with rheumatoid arthritis. Their work has shown that immunologic mechanisms are operating in the disease and play an important role in its development. It now appears that the rheumatoid factors are large, hitherto unknown antibodies which have been produced by the body as part of its defense mechanism. The rheumatoid factors behave like autoantibodies in that they react with a certain fraction of the patient's own gamma globulin, possibly because that gamma globulin has undergone some alteration that has made it antigenic. The nature of this "alteration," which could be the aftermath of an infectious process, the result of hereditary factors, or a combination of both, is yet unknown and subject to current investigation.

Research has been developing along two main paths of interest, the immunologic and the genetic aspects of the rheumatic diseases. One of the continuing studies at the Institute, and one which has recently turned up a rather striking finding, is directed toward families of patients with Sjogren's syndrome, a disorder often accompanied by rheumatoid arthritis. Earlier work had shown that these patients had a high frequency of abnormal circulating antibodies, and the investigators followed this up to determine whether their relatives also showed this high frequency.

Analyzing blood samples from "normal" blood relatives of the patients, the NIAMD scientists found that these relatives often had a variety of hidden or ignored manifestations of Sjogren's syndrome and abnormal circulating anti-

bodies. The closer the hereditary relationship to a patient with Sjogren's disease, the more frequent or severe were these manifestations. These findings suggest that a genetic mechanism is operating in the disease, and that the full genetic endowment leads to the frank disease while a partial genetic endowment may result in only partial manifestations among blood relatives.

The striking finding that I referred to are that four of the patients with Sjogren's disease being studied during the past year at the Institute developed malignant lymphomas, cancers affecting the lymphatic system. The unusual association in the same patient of these two uncommon diseases could not be ascribed to mere coincidence. Various clinical and laboratory features distinguish these patients from the usual patient with Sjogren's disease and most important are the alterations in their immune globulins. These alterations, observable in the alpha and beta-2 globulin fractions of blood proteins, are being examined most closely at the present time to uncover any possible relationship existing between autoimmunity and malignancy.

Another investigation of interest has been the first stage of a unique "population" study of arthritis in the United States, carried out among the Blackfeet Indians in Montana. The second half of the study will be carried out among a southwestern Indian tribe in Arizona. Results of the Blackfeet study suggest that the predisposing causes of rheumatoid arthritis may differ among racially different groups. The work has lent support to the concept that there may be two types of rheumatoid arthritis—acquired and inherited. Several surveys in recent years, both in this country and in Europe, have uncovered familial aggregations of rheumatoid arthritis and the rheumatoid factors, and these findings have been interpreted to indicate that the occurrence of both disease and factors was genetically determined. The Blackfeet study, however, revealed no such familial aggregations and suggests that among the Blackfeet the occurrence of the disease may be influenced or determined by environment, rather than inheritance.

Gout is another of the rheumatic diseases which I would like to mention briefly since some major advances have been made in this area during the past decade. Indeed, gout can be the best controlled of all the rheumatic diseases at the present time. This age-old disorder was once thought to be the result of overindulgence in food and drink, but it is now known to be caused by an inherited defect in body chemistry. This defect leads to an accumulation of uric acid in the body, and recurring painful attacks of gouty arthritis.

For hundreds of years physicians have been soothing these painful attacks with colchicine, a drug that is so specific for gout pains that its effectiveness is considered a means of diagnosis of the disease. But the precise action of the drug has been a mystery, since it does not affect the level of uric acid in the blood.

Recently, NIAMD scientists have discovered that the drug interferes with the action of white blood cells, which engulf and destroy invading bacteria. This process is known as phagocytosis, and in the case of gouty attacks, the object of the phagocytosis is urate crystals which have formed in body joints. The phagocytizing action initiates a vicious cycle of pain, inflammation and new crystal formation as the white cells engulf the urate crystals. The NIAMD research has shown that colchicine acts in this situation by diminishing the metabolic activity of the white cells, thus breaking the pain-producing cycle of urate crystal formation and inflammatory response.

PROGRESS IN METABOLIC RESEARCH

Metabolism is an almost boundless research area which is being intensively studied by Institute scientists and grantees. Some of the diseases in this area, like diabetes, are well known and frequent while others, such as alcaptonuria and phenylketonuria, are relatively rare. In view of the fact that "metabolism" is the term given to the sum total of multiple chemical reactions taking place in the body, it is easy to see how wide a field metabolic research covers.

Diabetes.—Of all the metabolic diseases, diabetes is probably the best known since it affects so many people. The disorder involves a derangement in the metabolism of fats and carbohydrates and of that portion of food protein which is used as energy-yielding material or "fuel." In diabetes there is a breakdown in the normal balance between carbohydrate and fat metabolism, and much has been learned about normal metabolism by studying these abnormalities.

From the patient's point of view, the continuing advances being made in the treatment of diabetes constitute one of the brightest features of contemporary medicine. As a result of these developments, such as the discovery and widespread use of the new oral antidiabetic drugs, the outlook for persons with diabetes has improved materially in recent decades.

The first of the oral drugs was made available in 1957, by the pharmaceutical industry, and several additional drugs are now in use. They have replaced regular insulin injections in more than a third of the Nation's diabetics, and although there are still many questions about their activity, it is now generally accepted that their most important action is to stimulate the beta cells of the pancreas to release more insulin into the bloodstream. Within the past year NIAMD grantees have reported on their results with two additional drugs which have been synthesized and which incorporate novel structural changes. They too have been found effective in diabetics, though they are not dramatically different from earlier ones. The value of having additional drugs lies in the fact that with prolonged use, patients may become refractory to one drug, but will still respond to others if they are available.

In other clinical work in diabetes I would like to mention the emerging concept of "prediabetes." It has been expressed in the statement: "Before you are born, you are prenatal; before you are diabetic, you are prediabetic." and it refers to the belief that impaired carbohydrate metabolism as diagnosed by the standard glucose tolerance test for diabetes is actually one of the later changes to occur in the diabetic, not one of the first ones. From a genetic standpoint a person is probably prediabetic at birth, though he may continue to have a normal glucose tolerance test for years.

Since it is conceivable that other chemical or perhaps anatomical changes may antedate abnormal blood glucose levels, investigators have been interested in the search for such early changes. If they could be detected prior to any observable disturbance in glucose metabolism, it might be a better time for instituting treatment in the hope of preventing progression to frank diabetes. One group of Institute grantees has devised several tests, including photography of blood vessels in the eye, and electron microscopy of ear lobe biopsies; early results indicate that they may have value in detecting the prediabetic. In related work, other grantees have found the nondiabetic obese subjects have abnormally high levels of circulating insulin after glucose administration, suggesting that obese subjects, though they do not exhibit the high blood glucose levels of the diabetic, may require compensatory, increased amounts of insulin to maintain such a normal blood glucose picture. This finding, and those from another grantee study which revealed a high incidence of diabetes during pregnancy, have provided important leads for early recognition of the disease in the obese and in pregnant women.

One of the benefits of the discovery of the oral drugs has been the increased interest they have engendered in basic problems related to diabetes. One of particular interest to NIAMD scientists involves the abnormal occurrence of amino acids in the urine of diabetic patients. This disorder has been reported by some investigators to occur in all diabetics, other researchers have found it only in some. What relationship it has to diabetes is still unknown, but a full disclosure of the mechanisms behind it may have an important bearing on the whole diabetes problem. Institute studies are now underway in both diabetic patients and normal volunteers to see how amino acids are handled by the kidneys, and what role, if any, insulin plays in the kidney's reabsorptive processes.

Histidinemia.—In other metabolic research, tiny slivers of skin clipped with nail clippers from the fingertips of children have allowed NIAMD scientists to pinpoint the cause of a newly discovered inborn error of metabolism. The disease is histidinemia, first detected by physicians in Canada within the past year and now shown by NIAMD investigators to be due to the inherited absence of one of the body's many enzymes. The missing enzyme is histidase, needed for the metabolism of histidine. Because of the biochemical similarity between histidinemia and a more serious disorder of body chemistry, phenylketonuria (PKU), the first cases of the new disease were picked up during diagnostic studies for PKU, a disease which is known to cause severe mental retardation if untreated.

The natural course of the new metabolic disease is yet to be learned, since none of the histidinemic patients is over 8 years old, but the only serious clinical manifestation of histidinemia seems to be a speech defect reported in four

of the first five known cases. Study of a large number of such patients is needed, and consequently a collaborative project has been started by NIAMD scientists with geneticists from the National Institute of Dental Research to screen speech clinics at schools and universities for undetected cases of histidinemia.

Cystic fibrosis.—Another disease of considerable interest is cystic fibrosis, a grave disease of children, adolescents, and young adults. It is thought to be caused by an inborn error of metabolism, a basic defect which produces a widespread disturbance in certain exocrine glands, the sweat, tear, and salivary glands, and many of the mucus-producing glands of the body. It is a highly fatal disease in which chronic and progressive pulmonary disease is the most critical development. Since over 90 percent of the deaths occur because of the lung involvement, trials of newer antibiotics and bronchial mucus-dissolving agents are an important aspect of current research.

In NIAMD's pediatric metabolism branch, attempts to discover the basic defect in cystic fibrosis involve both biochemical and immunological methods. Sensitive screening techniques are being used to locate any abnormal constituents common to all the organs and tissues of cystic fibrosis patients.

A well-known feature of the disease is the abnormally high levels of salt (sodium and chloride) in the sweat of these patients and this defect is the object of many studies. One of these involves the detection of individuals who are heterozygotes for the cystic fibrosis gene; these are persons who carry a partial genetic endowment for the disease but do not display the full gamut of clinical symptoms characteristic of the disorder. Recently it has been reported that there is a striking difference between normal subjects and such heterozygotes (or carriers) in their sweat electrolyte response to stress situations such as exposure to heat, dietary salt restriction and administration of various steroid hormones, and work is actively underway at NIAMD to clarify this pattern of response. Not only might this have great theoretical importance in helping to identify the defect in the sweat glands, but also from a practical standpoint it may clear the way for the development of a test for the recognition of the heterozygous carriers. The value of such a test can be readily understood when it is realized that 2 to 5 percent of the general population are thought to carry the genetic trait for the disease.

Among studies on cystic fibrosis, mention should be made of a finding by grantees at Northwestern University Medical School and Chicago Medical School. They discovered that these patients had a hitherto unknown deficiency of a fat-splitting enzyme, lipoprotein lipase, an enzyme that is normally active in the blood.

In addition to the specific diseases that I have singled out, much research continued on basic problems in metabolism and closely related areas. A major field of interest is the biochemistry of the thyroid gland and its hormones, and such studies as the synthesis of thyroxine and its transport in the blood are being pursued. Work has begun at the Institute on the isolation of the specific thyroxine-binding proteins from human serum, since the nature and properties of such binding proteins are of widespread interest and practical importance.

In previous years you have heard about our studies on bone metabolism, and the use of high calcium diets in the widespread disorder osteoporosis, and to offset the bone thinning effects of the corticosteroid drugs in rheumatoid arthritis. These and many other studies are continuing because of the complex difficulties these serious problems present and because of the considerable numbers of our population with thin or fragile bones from various causes.

Before leaving the general area of metabolism, there are two final developments worth mentioning, one involving the detection of the use of narcotics and the other concerned with the laboratory synthesis of one of the body's major hormones. In the first, NIAMD scientists have developed a method that promises to be of value in studying, among other aspects of the use of narcotics, the relapse rate of narcotic addicts. This is one of the major areas of research on addiction, and the NIAMD work has provided a rapid and sensitive method for detecting various narcotics in urine samples. It utilizes the relatively new technique of thin layer chromatography and, in comparison to older methods which took over 24 hours, can be conveniently completed in 4 to 5 hours. It will detect as little as 5 to 10 micrograms of narcotics or their metabolites and with modifications appears to be equally as rapid and sensitive for barbiturates, tranquilizers, and antihistamines. Thus, in addition to its research value, the procedure will be a valuable tool in toxicology and forensic medicine.

The other study of interest involves ACTH (adrenocorticotrophic hormone), the pituitary-produced hormone which stimulates cortisone production in the body. You may remember hearing in past testimony about the first successful synthesis of ACTH which was achieved in 1960 by Institute grantees at the University of Pittsburgh. The synthetic hormone, constructed from 23 natural amino acids, has the full biologic activity of natural ACTH, and its synthesis, which culminated many years of research by both the Pittsburgh group and grantees at the University of California, ranks as one of the major biochemical accomplishments of the past decade.

Since then, they have continued to move ahead. From their initial work the grantees felt confident that the techniques they had developed would be useful in producing tailor-made hormones which had specific desirable characteristics of ACTH but which might be free from any other unwanted effects. Current reports indicate that they are making progress in this area. They have synthesized and made available a number of ACTH-like peptides which display a variety of significant biological actions, for studies by qualified investigators.

GASTROENTEROLOGY—10 YEARS OF CHANGE

Among the medical specialties, gastroenterology has undergone one of the greatest relative changes within the past decade. It is a field of enormous scope, in terms of the number of people affected by disease. Encompassing all the diseases of the digestive tract, gastroenterology includes such well known disorders as peptic ulcer, regional ileitis and ulcerative colitis. During the past 10 years, newer techniques of studying digestive physiology, methods of obtaining biopsy specimens, and the use of isotopically labeled materials have all helped to put research in this area on a sound, scientific footing.

Gastroenterological research is in a state of dynamic transition from the mild interest of a few years ago. A significant factor in this renaissance has been the granting of increased funds for research by the Institute. This support has been effectively used. During the past year, for example, grantees have been able to produce rapid healing of duodenal ulcers in a substantial number of patients by freezing the stomach mucosa for short periods of time. The freezing is accomplished by a subzero cooling liquid circulated through a balloon placed in the stomach. Only initial studies have been reported thus far, so that it is premature to suppose that this may at last be the simple and effective treatment that has too long been sought for ulcers. However, if additional studies bear out the usefulness of the new technique, it may avoid the need for surgery in many duodenal ulcer cases.

Another development of interest, which indicates the cross-fertilization taking place between the physical scientists and the medical scientists, has been a new diagnostic tool for examining the gastrointestinal tract. This flexible endoscope employs fiber optics for its viewing elements and thus can be bent to follow the curves in the digestive tract. It makes possible direct examination of many areas that had previously been inaccessible to the conventional rigid gastroscope. This tool was developed by a scientist who is now a grantee of the Institute and who is utilizing it for much-needed direct studies of the gastrointestinal tract. At present he is adapting and modifying the flexible endoscope for other specialized diagnostic uses.

At the NIAMD, one focus of attention has been on the biochemical aspects of the digestive process, and the work on Whipple's disease is a prime example of progress in this area. Whipple's disease is a grave metabolic disorder in which there is loss of weight and strength associated with a defect in fat absorption by the intestine. Frequently, these patients also exhibit abnormally low levels of albumin in their blood, and the cause of this hypoalbuminemia has now been discovered by Institute studies. The use of radioactively labeled albumin enabled scientists to determine that in these patients there was heavy leaking of albumin from the blood into the gastrointestinal tract.

The situation was found by NIAMD investigators to be readily reversible. With proper treatment, including the use of adrenocortical steroid hormones and antibiotics, the intestinal loss of protein subsided and blood albumin levels returned to normal. This study in particular points up some of the unique characteristics of the Institute's clinical program, for whereas Whipple's disease is sufficiently rare that a single institution may never see one case, NIAMD scientists have now studied six cases intensively. Study of this rare disease is important because it may yield clues to the problem of malabsorption, a condition present in numerous other gastrointestinal disorders.

HEMATOLOGY

Hematological research is assuming an increasingly important role in the program activities of the Institute. Anemias of various types, and clotting disorders like hemophilia are but a few of the multitude of diseases known to affect the blood and blood forming elements. Considerable progress is being made at the Institute in discovering the basic mechanisms that are operating in some of these disorders. As in all scientific work, however, each new finding poses additional questions.

Recently, NIAMD scientists pinpointed the cause of a serious blood disease which occurs in newborn infants, a disorder called thrombocytopenic purpura. They found that most cases of infant purpura—characterized by bleeding and a lack of blood platelets—are due to antibodies formed in the expectant mother against a different platelet type in the unborn child. The infant's type of platelet is inherited from the father, and because it is foreign to the mother, provokes the formation of antibodies. The mother's antibodies are transmitted to the infant through the placenta, and, by destroying his platelets, precipitate a bleeding disorder.

The work has led the researchers to identify at least seven different "types" of human platelets, the differences being similar to the differences in types of red blood cells which are responsible for the well-known blood groups.

Continuing work has shown that mismatching of platelets can cause ill effects not only in newborn infants, but also occasionally in children and adults who receive transfusions. It was found that platelet antigens frequently are mismatched when blood transfusions are given and may provoke antibodies which destroy platelets in subsequent transfusions. Destruction of platelets by these antibodies may be the cause of some hitherto unexplained transfusion reactions.

In other clinical research, grantees at the University of Washington School of Medicine have greatly prolonged the useful lives of patients with fatal kidney disease by using new techniques associated with the use of the artificial kidney. These techniques involve maintaining ready access to the patient's circulatory system by inserting in-dwelling plastic valves in the blood vessels of the forearm or in the abdominal wall, thus allowing frequent and easy attachment of the patient to an artificial kidney.

This machine, designed many years ago, sends a patient's blood through lengthy thin plastic tubing in a special bath and thereby removes harmful body wastes which would ordinarily be removed by the patient's own kidneys if they were normal. To date the artificial kidney has been extremely valuable, and in many instances, lifesaving; but could only be used in temporary (few days to 2 weeks) shutdown of the kidneys, because of the necessity for making a new surgical attachment between the machine and an artery and vein each time the machine is used. Since the new plastic valve devices developed by the Seattle investigators can remain permanently at the surface of the patient's body, the artificial kidney may be readily attached and will permit hemodialysis therapy on a regularly scheduled basis to patients who had lost their kidney function, without which life is impossible.

The investigators' increasing experience with the method has led to many improvements in hemodialysis technique (variation in rates of flow and duration of dialysis) and in design of the artificial kidney, which have increased the safety and effectiveness of the procedure and prevented death in a growing number of patients with chronic renal failure. During the past 2 years, a number of patients have benefited from this lifesaving method of treatment and it has considerable potential for future care of patients with serious kidney disease.

INTERNATIONAL NUTRITION RESEARCH

In addition to nutrition research carried out in its laboratories in Bethesda, the Institute supports the research components and research-related activities of the Interdepartmental Committee on Nutrition for National Defense (ICNND). During the past 2 years the international nutrition activities of the Committee have been accompanied by a measure of research work, much of which may be characterized as epidemiologic—the determination of facts concerning the incidence, distribution, and interrelationships of nutritional disease in different populations and geographic, climatic, and economic environments. This work has produced a variety of meaningful new information of considerable research interest in the United States. Thus, for instance, a study in South Vietnam of the relationships between goiter incidence, dietary iodine intake, and

the ratio of iodine and creatinine in urine has contributed a new and apparently reliable index of dietary iodine intake. In other studies evidence has been uncovered for a possible and hitherto unsuspected role of vitamin E in the formation of red blood cells, and additional knowledge has been obtained concerning the human requirements for a number of vitamins. This type of epidemiologic research has not only demonstrated a concrete relevance to domestic health problems and health needs, but has also been productive in revealing pertinent areas and new directions for the application of biomedical research.

PROSPECTS AND PROBLEMS FOR THE FUTURE

Returning now to the broader view of medical research, I would like to describe briefly our plans for future progress in the work of this Institute. Within the laboratories at Bethesda, in view of the fact that we have fully activated the laboratory space available to us, we look forward at the moment to only minor changes in total numbers of personnel. In an organization of more than 200 investigators, however, we must expect change and turnover. The significant aspect of this process is that steadily improving quality and capability is our aim, an aim in which we are in close and continuing competition with numerous universities and medical centers aided also, in part, by NIH funds. For successful continuation of our efforts and accomplishments in high level intramural research, therefore, it is paramount that we rapidly and continually improve our capacity to attract and hold the quality investigators needed.

The major part of our efforts, of course, will be expanded in the support of research in the university and other medical centers of the country. Here again the key to important and valuable research for our Nation's health is highly trained, skilled, and imaginative scientific manpower. Significant advances in the treatment or prevention of our major illnesses will be achieved by better and more intensively trained investigators. It is for this reason that we continue to emphasize the need for expanding support for training and at the same time continually seek ways to develop and support new and more effective training programs. One of these new programs, intended for intensification of the training of clinical investigators, will be briefly described later on.

As you know, there are two major mechanisms through which the Institute supports advanced and specialized training of young physicians and scientists—training grants and postdoctoral fellowships—and over the years these programs have been of tremendous value. One indication of their value comes from a recent survey of former Institute fellows, aimed at eliciting their present occupations and their professional growth since their Institute supported training. This survey showed clearly that an overwhelming majority of these scientists are presently engaged in research and teaching and have continued to be productive in these areas since their training period.

The new NIAMD program geared to the future is an experimental one to develop more effective ways of training young men and women for careers in clinical research. The existing methods of training medical specialists and research workers have accomplished much, but it is possible that in various ways in certain centers they may be improved upon. The Institute's experimental program of training for clinical investigation will enable a limited number of selected institutions to attempt to revise and strengthen their training methods for clinical investigators and make these methods more responsive to the present needs of medical research.

The purpose of the NIAMD program is to provide a means of strengthening, intensifying, and possibly condensing the training period between the third year of medical school and the third to sixth year after medical school graduation, during which time period the young clinical investigator is developed. For higher quality studies of disease processes in patients the relatively high clinical proficiency now provided by the residency system must be—for certain, selected, highly qualified individuals—impregnated with training experience in high quality laboratory research techniques and procedures and understanding of the sophisticated research method.

In terms of research activity itself, it is obvious that due to substantial support of the research grant program our knowledge has been vastly multiplied during the past decade and is still enlarging at an ever-increasing rate. One might say, in anthropological terms, that the culture base has been extended. The longer the base, the greater are the opportunities for recombining items already in existence, and this recombination is the basis for developing new

ideas and new knowledge. New ideas and new knowledge are developed at a faster rate than ever before; simultaneously, we are becoming increasingly aware of what has been called the communication problem. As a direct result of the successful expansion of biomedical research, a tremendous amount of new scientific information is being produced which must be conveyed and made available to active investigators, for fertilization of their research efforts, and to the community of practicing physicians in order to bring the benefits of this research to the bedside of the patient at the earliest possible moment. Considering the magnitude of new unfolding knowledge and the large audiences to which this knowledge must be conveyed to be of value, the communication problem may indeed become very serious unless vigorous efforts are expended to meet it.

At the Institute, we are acutely aware of this need and are deeply committed to special efforts on this matter. We have extended major financial support to the establishment of a comprehensive diabetes abstract-translation-microcard-retrieval system which combines facilities for collecting, abstracting, and translating all scientific diabetes data published anywhere and its incorporation into an electronic storage and retrieval system dedicated to the support of current and future research efforts in diabetes. We have just committed ourselves to a project devised to establish a basis for improved storage, retrieval and dissemination of arthritis research data through application of new communication methodology. We are carrying out a major program of communications which includes the stimulation and promotion of personal interchange between scientists through conferences and symposia, the selective support of primary and secondary scientific publications, the preparation of comprehensive scientific exhibits and pertinent literature on the latest advances in specific diseases, which are being brought to the attention of thousands of practicing physicians, the production of motion pictures for information and education purposes, the maintenance of a clearinghouse for information about analgesic and narcotics drugs, and the constant screening and translation of foreign research reports, including those from the Soviet Union.

Recently a new Office of Scientific Communications has been established at the Institute to provide well-directed and vigorous impetus to our ongoing efforts in medical and scientific communication.

And so we approach another year. We are making continuous progress, some of it more dramatic than the rest, some of it more immediately perceived than the rest, but we have come a long way and there are now many exciting possibilities opening to us. In order to continue our important programs, Mr. Chairman, I am submitting a request for \$114,717,000 as compared with the operating level of \$100,798,000 for 1963. The proposed increase for 1964 will provide for an estimated 368 additional research projects in arthritis, diabetes, gastroenterology, and various metabolic diseases. This request for 1964 is distributed among program activities as follows:

Grants:

Research-----	\$82, 513, 000
Fellowship-----	4, 019, 000
Training-----	14, 420, 000
Subtotal, grants-----	<u>100, 952, 000</u>

Direct operations:

Research-----	11, 307, 000
Collaborative studies-----	713, 000
Review and approval-----	1, 469, 000
Program direction-----	276, 000
Subtotal, direct operations-----	<u>13, 765, 000</u>

Total, 1964 appropriation request-----	114, 717, 000
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COMPARISON OF 1963 AND 1964 BUDGETS

Dr. WHEDON. Mr. Chairman and members of the committee:

The 1964 budget request for arthritis and metabolic diseases activities which is before you is for \$114,717,000 as compared with the operating level of \$100,798,000 for 1963.

The past year has seen a strengthening of basic and clinical research both in the Institute's laboratories and in those institutions receiving Institute support. Progress in basic research has been significant, especially in the area of genetics and understanding of the chemical mechanisms that permit inherited characteristics to be transmitted from generation to generation. Studies in gastroenterology, in diabetes and other metabolic diseases have produced some of the most encouraging advances ever achieved in a single year. In the major area of the rheumatic diseases, a clearer picture has emerged of the disease process in gout and of the relationship between environmental and genetic factors.

The proposed increase for 1964 will provide for an estimated 368 additional research projects in arthritis, diabetes, gastroenterology, and various metabolic diseases. The request for 1964 is distributed as follows: \$82,513,000 would be allocated for research grants; \$4,019,000 for fellowship grants; \$14,420,000 for training grants; while direct research at the Institute and supporting services will require \$13,763,000, yielding a total of \$114,717,000.

Mr. Chairman, if I may, with your permission I would like to describe some representative research activities and accomplishments.

Mr. FOGARTY. Sure, we would like to hear them.

Dr. WHEDON. Then, as an item following that, or at a later time, I would like to say something about accomplishments in our training area.

DEVELOPMENT OF TESTS FOR PREDIABETES

The first of the accomplishments I wish to describe is one which we believe is a very important advance in our understanding of diabetes, one which should lead to real progress. I refer to a new concept that there is a state of prediabetes in a diabetic patient long before he develops the clinically evident disease of diabetes. The concept that we have had up until the present time is that diabetes appears rather rapidly, that is, over the course of a few weeks or months, in an apparently otherwise normal individual; and the new diabetic then rather rapidly develops the symptoms related to intolerance to sugar, usually excessive loss of sugar, and of water, in the urine.

But now we have evidence that the diabetic is predetermined to have this disease at conception by genetic factors and then lives for either a few or for many years apparently perfectly normal, before he develops the clinical disease.

Now, the work that was done to develop this new concept is something like this: Knowing that a person is bound to have diabetes if both of his parents have diabetes, investigators at the Deaconess Hospital in Boston made a variety of tests and observations of 54 such individuals, who did not have diabetes but were certain to develop it because both of their parents had diabetes.

The significant thing that they found was that there are certain changes in the tissues of these individuals' bodies, without any change in carbohydrate metabolism—even changes in carbohydrate metabolism that might have been picked up by some of the special tests that you have heard described previously, using cortisone.

The tissue changes that they found were of two sorts: One was, by observation of the blood vessels in the ocular conjunctiva—that is, of

the inner side of the lids of the eye—where examination and then photographs were made of the veins and arteries in the lids, and whereas the normal ratio of the diameter of the veins to the diameter of the arteries is 2 to 1, in these prediabetic individuals the ratio was 4 to 1. In other words, the veins were distinctly larger than in the normal individual.

The second tissue change was found by taking a small bit of tissue from the ear lobe, a biopsy of ear lobe tissue, and then examining this tissue, not under the regular microscope but under electron microscopy in which the scientist is able to look down at the tissue with a tremendous degree of magnification. They found clear-cut evidence that in the minute venules—that is, the tiniest blood vessels—the walls of these vessels showed dilatation and leakage, findings that are not found in the normal individual.

Now, the intriguing and significant aspect of these findings is the possible value of using these two tissue examinations as tests for early detection of this prediabetic state in all sorts of individuals, not just the individuals we know would develop diabetes; and then undertake to try the effects of early institution of dietary management or other forms of treatment in an effort either to delay the onset of the clinical state of diabetes or perhaps even prevent it.

This would be very important, of course, because we would then hope to be able to modify successfully the various complications of cases of diabetes which occur when diabetes continues for over a number of years.

SPECIAL REPORT ON DIABETES

Mr. Chairman, we have prepared a special report of our progress in diabetes which we would be glad to submit.

Mr. FOGARTY. Put that in the record.

Dr. WHEDON. Yes, sir.

(The material follows:)

SPECIAL REPORT: DIABETES

During 1963, an estimated 75,000 people in the United States will be newly diagnosed as diabetic. Since the first diagnosis of diabetes in the 3d century B.C., men have attempted to control this disease with special diets; but, until the 20th century, when insulin was discovered, their attempts were largely ineffective.

Borrowing partially from his ancient brother, the modern diabetic relies on special diets supplemented by insulin or oral drug therapy, as a frontline defense against a disease once thought to be a "melting down of flesh and limbs." The recently increased awareness of the importance of the prediabetic state in individuals who later develop the symptoms of diabetes is a major development which may alert research scientists and practicing physicians to the possibility of earlier control and even delay or, perhaps, preventing onset of the disease.

Diabetes is a serious metabolic disorder, a built-in error in the body's metabolism, which affects individuals predisposed to the disorder by their hereditary background. The obvious defect in diabetes is the body's inability to metabolize carbohydrates normally. As a result, the diabetic is unable to utilize efficiently the carbohydrates he consumes and to turn them either into heat and energy needed for normal body functioning or store them in the form of glycogen. Instead, the carbohydrates, converted into glucose, accumulate in blood and tissues and spill over into the urine. Primarily, this occurs because of a diminished supply or availability of insulin, a hormone produced by the pancreas, although many other factors are now known to be involved. Not only may there be a decreased production of insulin but there

may also be impairments in the way insulin acts. Also, disturbances in the metabolism of fats and proteins accompany the defect in carbohydrate utilization. During the past year studies conducted in Bethesda or supported by this Institute and carried out in other medical centers have continued to increase the body of knowledge concerning this complicated disease and have contributed methods of detecting the prediabetic state.

TREATMENT

In 1921 the now famous team of Frederick Grant Banting and Charles Best—following up the 18th century work of Thomas Crawley who first suggested that diabetes may follow injury to the pancreas—discovered insulin and thus began a new era in the history of diabetes. The success of the first clinical trials with insulin in 1922 assured maintenance of life for the diabetic patient.

The development and refinement of both rapid and slow acting insulins followed, and their selective use (or that of a mixture of the two) was found to be effective depending on the individual case. Insulin injections have so far proven irreplaceable for children and young adults—the two groups who develop the most severe cases of diabetes; these individuals apparently cannot produce enough insulin to overcome their metabolic defect. In the older patient the onset of diabetes is usually gradual and in some cases control can be achieved by strict diet, or through marked weight reduction.

In many cases, weight reduction alone can adequately control diabetes. Of the estimated 75,000 people who will be diagnosed this year, most will be in the fifth or sixth decade of life. Six out of every seven patients who are over 40 at the onset of the disease are also overweight, and in these patients carbohydrate tolerance tends to become normal as their weight is reduced to a point slightly below normal limits.

A revolution in the treatment of maturity-onset diabetes has occurred in recent years through the use of the oral antidiabetic drugs. The first ones, the sulfonylurea compounds, were developed in 1957, and since then several others including the nonrelated, but highly effective drug phenformin have come into use. They now replace insulin injections in more than one-third of the Nation's diabetics. Two new oral drugs were synthesized recently by the pharmaceutical industry and were reported effective in diabetics by NIAMD grantees who evaluated the drugs in clinical trials. Though not significantly more effective than the ones now in use, these new compounds may be useful in individuals who become resistant to the older drugs. Physicians are hopeful that more and more of the maturity-onset diabetics may be controlled with the aid of oral drugs.

Although the "control" of diabetes has improved dramatically during the last half century, it is still the seventh highest killer among diseases in the United States. In the older diabetic who has had the disease for many years, degeneration of small blood vessels in the eyes and kidneys, and an early onset and rapid progress of systematic atherosclerosis are expected complications. Coronary atherosclerosis is also frequent in the older patient, and other complications include persistent skin infections and diabetic neuropathy. What effect the newer forms of drug therapy may have on the course of such complications remains to be seen.

PREDIABETES

The evolving concept of prediabetes may lead to a new era in diabetic research and treatment. Positive diagnosis of prediabetes could mean earlier treatment for the patient and the hope of delaying or possibly preventing the eventual emergence of frank diabetes.

Impaired metabolic handling (intolerance) of carbohydrate has been considered initial evidence of diabetes, but researchers now believe this is probably one of the later manifestations of the disease and that the individual has been "prediabetic" long before carbohydrate intolerance is detected. Generally, prediabetes is thought to be that period in the life of the individual genetically predisposed to diabetes during which compensatory mechanisms permit the subject to function normally on the surface, though he may concurrently sustain hidden physiologic and morphological damage. Symptoms of frank diabetes (excessive thirst, hunger, and the appearance of sugar in large amounts in urine) do not emerge, therefore, until these substitute mechanisms can no longer do the job. Scientists believe that this prediabetic condition exists from birth to the

diagnosis of active diabetes, and is not to be confused with a mild case of the disease.

Although the diagnosis of prediabetes must often be made in retrospect, there are some tests now being developed which may help to detect the condition. For the full diabetic state the standard glucose tolerance test is a sensitive index and is used to diagnose frank decompensated diabetes. A similar but more sensitive method, the cortisone-glucose tolerance test, is now used to detect diabetes-prone (but still compensated) individuals who do not register as abnormal in the normal test method.

During the last year, Institute grantees have devised a group of test procedures to find the prediabetic individual before his disorder becomes overtly manifest through onset of the clinical symptoms of diabetes. The procedures, which include photography of conjunctival blood vessels and electron microscopy of ear-lobe biopsies for recently discovered characteristic pathologic changes, provide new diagnostic tools which could enable early detection of prediabetic individuals. Electron microscopy of ear-lobe biopsy specimens from prediabetic subjects suggests that dilatation and leakage of minute venules, changes not present in normal control subjects, are the first morphologic evidence of diabetic derangement of the vascular system.

In other studies, NIAMD grantees have found that after intravenous glucose administration, nondiabetic obese subjects have a significantly higher insulin response, and subsequently sustain higher levels of circulating insulin than nondiabetic normal subjects. These findings suggest that obese patients require increased amounts of insulin to maintain normal blood glucose levels. The observations of the NIAMD researchers imply that obese subjects are in a "compensating phase" which requires that they secrete an abnormally high amount of insulin in order to maintain normal control of blood glucose levels. The study also indicates that measurement of serum insulin levels after a glucose load may serve as a useful diagnostic tool in diagnosing the diabetic trait prior to the development of frank carbohydrate intolerance.

A long-term study, by another NIAMD grantee, of unsuspected, asymptomatic diabetes in pregnancy has revealed an unexpectedly high incidence of diabetes during pregnancy. Screening of 20,070 women registering for prenatal care at 2 Boston hospitals disclosed a rate of overt diabetes in pregnancy 4 to 8 times higher than that observed among similar nonpregnant control subjects. The NIAMD investigator reported that diabetes could appear temporarily in pregnancy as long as $5\frac{1}{2}$ years before subsequent development of the full-blown disease picture. The development of overt diabetes at a later time among these patients makes them "prediabetic" beyond a doubt. This study suggests that such patients are ideally suitable subjects for study of diabetes mellitus while it is still latent, yet easily recognizable, and that gestational diabetes is an important diagnostic landmark for early recognition of the disease.

OTHER RESEARCH ACTIVITIES

Along with the attempts to perfect methods of detecting the prediabetic state, encouraging work is being done on other problems of diabetes. An electron microscopic study of the effects of the oral antidiabetic drug tolbutamide on the structure of pancreatic beta cells in the rat has shown clearly that the drug acts by stimulating the release of insulin from these cells. According to this study there is little difference between the insulin release mechanism triggered by tolbutamide or by an elevated blood sugar level. The NIAMD grantees found that the drug caused beta granules to be released from deep within the cell by an injection process. These granules, presumed to be made up of insulin, appeared to migrate to the cell surface where they fused with the basement membrane of the cell, which then ruptured, and released its granular contents into the extracellular space adjacent to a capillary. In other electron microscopic studies the investigators observed that an amorphous material was clumped by the beta cells before the formation of the granules; they believe that this material may represent a precursor of insulin.

A recent quantitative analysis, by another NIAMD grantee, of insulin release into pancreatic venous blood has shown that the pancreatic insulin response to glucose is much greater and longer in duration than the response to sulfonylurea drugs (the major group of oral drugs used in the treatment of maturity-onset diabetes). Glucose and three sulfonylurea drugs, infused intravenously, promptly initiated the release of insulin into the bloodstream. The response

to glucose was intense in magnitude and sustained; the response to the sulfonylurea drugs comparatively moderate and transient. Glucose appears truly "insulinogenic"; it not only triggers release of preformed insulin granules stored in the beta cells of the pancreas, but also generates formation and secretion of new insulin in proportion to the concentration of glucose in pancreatic arterial blood. Sulfonylurea drugs, in contrast, seem merely capable of releasing preformed, stored insulin and of effecting its rapid discharge into the circulation.

One of the many basic puzzles yet to be solved in connection with diabetes is the abnormal occurrence of amino acids in the urine of diabetic patients. This disorder has been reported by some investigators to occur in all diabetics, while other researchers have found it only in some patients. What relationship this amino aciduria has to diabetes is still unknown, but a full disclosure of its mechanisms may have an important bearing on the whole diabetes picture. Institute studies are now underway with both diabetic patients and normal volunteers to see how amino acids are handled by the kidneys, and what role, if any, insulin may play in the kidney's normal conservation of needed amino acids.

Another problem in diabetes treatment was further clarified this year by studies of chronic insulin resistance, a situation encountered in some patients who require unusually high doses of insulin to bring their blood sugar levels under control. Five "insulin resistant" patients at the Institute were successfully treated with adrenal cortical steroids resulting in a significant reduction of their insulin requirement. The effectiveness of the steroid drugs supports the idea that diabetics who require extraordinarily large amounts of insulin carry in their blood some type of antagonist or antibody to insulin. Thus they require huge dosages of insulin to overcome this blocking action before the administered hormone succeeds in controlling the patients' elevated blood sugar levels.

The elusive cure for diabetes is still the continuing goal of many research teams, and the achievements of the past year have added considerably to the basic understanding of the disease. Fortunately, the availability of new oral antidiabetic drugs permits easier and often smoother control of the disease in the maturity-onset individual, but full solution of the diabetic problem awaits clarification of the basic disease processes. Prime suspects among these basic processes are defects in the pancreas which may affect the formation or release of insulin, the existence of different types of insulin antagonists in the liver and peripheral blood, as well as immunologic mechanisms, all of which may serve to "bind" or inactivate the hormone. Future progress against diabetes will depend on establishing positive evidence for these suspected defects.

INCREASED UNDERSTANDING OF GOUT

Dr. WHEDON. The second accomplishment has to do with the disease of gout. We believe we have increased our understanding of this disease significantly. Now, although through the ages gout has shown a predilection for the brilliant and talented, and particularly for great statesmen of government, we hope that none of you gentleman will have personal experience with this disorder. Nevertheless, you should be on guard because of this relationship.

You are familiar, I believe, with the fact that studies which we conducted in Bethesda and by investigators whom we have supported in the past, have worked out by metabolic studies, using radioactive isotopes, that the accumulation of uric acid in the body of patients with gout is of two types: One due to overproduction of uric acid in some patients, and impaired kidney excretion of uric acid in others.

Last year, Dr. Daft, my predecessor, reported to you that Dr. Seegmiller of our laboratories in Bethesda, and his associates, had been able to determine the nature of the physiological event that takes place when a patient with gout suddenly develops an acute arthritic attack, which is extremely painful. He found that what takes place is the precipitation of uric acid crystals in the joint. He found this out

by injecting uric acid into the joints of patients with gout and also of individuals who were perfectly normal. He found, for example, that in either situation, when uric acid was injected into the joint, pain and inflammation occurred which in some instances was identical with that of a spontaneous attack of gouty arthritis.

This year in the new work which I wish to bring to your attention, Dr. Seegmiller has found the mechanism by which the drug colchicine works to interrupt and allay the attack of gouty arthritis. It does it by interrupting phagocytosis; that is, the engulfing of uric acid crystals by white blood cells.

Dr. Seegmiller's group showed this in two ways. He gave colchicine, a drug given by mouth, to patients with gout, then injected their joints with uric acid and found that these individuals who had received colchicine before the injection of uric acid had far less pain and less inflammatory change than they had if colchicine was not given.

By inserting a needle and withdrawing fluid from the joint at this point he found that in the patients who were not given colchicine, uric acid crystals would appear to be engulfed by the white blood cells but in patients who had been given colchicine beforehand, this engulfment did not occur.

The second way he worked this out was to set up in the test tube fluid from normal patients and patients with gout and add to each uric acid crystals and white blood cells. Here again, in the instances in which he added colchicine right to the test tube, to this mixture of joint fluid, uric acid crystals, and so on, the white cells did not engulf the uric acid crystals. I should add he also found that the action of colchicine was by a direct effect on the metabolism of the white blood cells. It interfered with their uptake of glucose and with the production of carbon dioxide and lactate, which are part of the normal processes of the metabolism of white cells.

We hope from this that studies will lead ultimately to solution of the relatively basic problem of what causes uric acid to be precipitated in the joints leading to the actual attack. But meantime, I would like to remind the committee, because I believe it has been reported to them previously, that gout is one of the arthritic diseases for which we have the best techniques of management. If a patient is under good medical care and receives certain drugs which will increase the excretion of uric acid, this will keep the blood level of uric acid at a relatively safe level, and we also have colchicine which is a very effective drug in aborting an acute attack, if this should occur.

MOLECULAR DISEASE RESEARCH

Mr. Chairman, I would like to mention one other rather significant advance which we have made; this is in the area of the metabolic diseases and rather specifically in the group of diseases which we have termed "molecular." We call them this because these are the group of diseases in which an important enzyme is either missing or is defective, and as a result of this enzyme disorder, a functional, clinical disorder occurs in the individual.

IDENTIFICATION OF HISTIDINEMIA

You have heard in the past of two of these diseases: galactosemia and phenylketonuria. We can report now some very beautiful combined biochemical and clinical work by investigators in our Institute laboratories, which have clearly defined the metabolic error in a new molecular disease called histidinemia. This disease is so called because there is an excessive level in the blood of the amino acid histidine. The disease was first described only some 18 months ago by pediatricians in Toronto, who at that time were interested in learning more about phenylketonuria, another of these molecular diseases; they came across two children who gave a positive test in the urine by chemical tests that are used for the detection of phenylketonuria. But, although they showed a positive test for phenylketonuria, they had no degree of mental retardation, which was very unusual. So they examined these patients further and found that the level of the amino acid phenylalanine in the blood was perfectly normal, whereas it would have been expected to be elevated for phenylketonuria; but what they did find that was positive was that another amino acid, histidine, was increased in the blood.

Then a few months later, grantees of this Institute at Temple University in Philadelphia found a third case and worked the patient up fairly carefully and suggested that the metabolic defect might be the lack of the enzyme histidase, the enzyme necessary to break histidine down into important small units necessary for the synthesis of other important chemical substances in the body. Then, within the past year, our own Dr. LaDu and his associates completed the work on understanding of the cause of this disease by showing the lack of the enzyme histidase in the tissues of two additional patients.

Now, ordinarily, in order to make a clear and absolute definition of the lack of an enzyme in the body, one would examine the liver for enzyme activity.

MR. FOGARTY. What is histidinemia? What does it do?

DR. WHEDON. I was just coming to that.

MR. FOGARTY. Excuse me.

HISTIDINEMIA SYMPTOMS

DR. WHEDON. I was just going to say that ordinarily one would examine the liver of these patients, but these two children that we had under examination appeared to be entirely too normal to subject to removal of tissue from the liver. Our investigators thought, however, that there was a possibility that the enzyme might be lacking in the skin, and so by just shaving the tips of the fingers, they obtained sufficient skin tissue, both in the patients and in normal individuals, to examine for the presence of histidase, the missing enzyme. They found that it was indeed missing in the patients and present in abundant quantities in normal individuals.

Now, as to your question, Mr. Chairman, all five of these patients are perfectly normal mentally, but what they have is a speech defect, and it is a rather peculiar speech defect characterized by what is known as a "short auditory memory." Most of us are able to speak tolerably well and continue a logical conversation, because we hear what we say

over a sufficient period of time, to add on successively phrases and words in a proper sequence; but these individuals apparently are unable to hear their voice for more than a split second, and so cannot put together significant verbiage to make appropriate statements.

The extent of this disease is unknown, and our investigators have begun a collaborative project with geneticists in the Dental Research Institute and with the speech clinics at the University of Maryland, and in Montgomery County, to examine patients who have speech disorders, to see if they have this molecular disease.

Mr. Chairman, either at this time or later I would like to talk further about developments in our training grants program.

Mr. FOGARTY. In histidinemia, all of these patients that they worked with had this peculiar speech defect?

Dr. WHEDON. Four of the five, so far.

Mr. FOGARTY. I see. But you really do not know the extent?

Dr. WHEDON. We do not know the extent of the disease until we have examined more patients who have this speech defect; and, of course, at this stage of our knowledge of the molecular diseases, it is far too soon to know what we can do to correct the disease.

Mr. FOGARTY. Go ahead, Doctor.

TRAINING MEDICAL MANPOWER

Dr. WHEDON. As you know, we feel very strongly that scientific manpower is the vital cog in improvement and extension of progress in the health sciences, and ultimately to the improvement of the health of the Nation. Specifically, we need highly trained, skilled, and imaginative manpower in the biological and medical sciences.

Now, over the past year we can describe three developments and plans for intensifying and improving the training of our medical research manpower.

EXTENDED LENGTH OF TRAINING PERIOD

The first of these developments is that we are undergoing efforts to extend the length of the training period of our individual trainees. We recently made a survey by communicating with our training grant directors and found that the average length of stay of a trainee on a training grant was approximately 1.4 years. This meant to us that a substantial number of our trainees were remaining in the training grant for only 1 year, and most of our consultants and experts in training feel that 1 year is entirely too short a period for the training experience to have lasting value.

So we are encouraging our training grant directors, when they select young physicians to go into research training, to undertake a longer period, 2 or possibly even 3 years, so that their experience will be much more meaningful.

TRAINING IN ORTHOPEDICS

The second training development is that we are undertaking extension of research training into the field of orthopedics. Orthopedics has been a subspecialty of surgery for many years. It has attracted, in the past, primarily individuals who were interested in

medical care of problems of the bones and joints. With recent awareness, however, that bone is a tissue which is very nearly as dynamic and full of life as many of the other tissues in the body, there has been an awakening of interest in research and greater understanding of bone problems by orthopedic surgeons. We are in the process of taking advantage of this awakened interest to undertake extension of training grants in research in the techniques that would lead to improving our understanding of orthopedic surgery.

TRAINING FOR CLINICAL INVESTIGATION

The third development, which we would plan to do next year as an extension of what we have begun this year, is the experimental program of training for clinical investigation. This is training of the young physician or medical student who is motivated to go into clinical research, rather than into private practice. At the present time we have numbers of well trained biochemists, and we have some very excellent clinicians. The individuals who have gone into clinical investigation thus far are individuals who have had a little training of each type and it has taken them altogether many years in order to reach a state of sophistication and real accomplishment in applying research techniques to the study of patients.

Now, the purpose of this new program of ours, in which we are cooperating, incidentally, with the new National Institute of General Medical Sciences, is to provide for certain selected individuals a means of strengthening, intensifying, and perhaps even condensing this period which generally extends from the third year of medical school on out to perhaps the fourth, fifth, or sixth year of experience past graduation from medical school.

In order to develop really higher quality studies of disease processes in patients, we think that the relatively high clinical proficiency which a young physician gets in several years of hospital training in our best centers ought to be supplemented with training experience in high-quality laboratory research techniques and procedures and in understanding of the investigative research method.

I wish to make clear, however, Mr. Chairman, that this is not to be a widespread program throughout all of our medical schools or affecting all of our house officers and residents, but merely for a limited number of highly selected individuals who we feel have a particular talent for research, probably, and have themselves expressed a great interest and desire to go into research, rather than into private practice.

This program is just getting underway this year, and we expect a gradual, careful extension next year.

Mr. Chairman, there are other developments I could talk about, but perhaps I should stop at this point.

Mr. FOGARTY. If it shows progress, go ahead.

TREATMENT OF PEPTIC ULCER

Dr. WHEDON. I think one of the very interesting things that has come out this past year as a potentially very significant development in gastroenterology is in the treatment of peptic ulcer.

It has been known all along that there are many factors which bring about ulcers, the skinning away of the lining of the duodenum which is the first portion of the intestine, immediately following the stomach; but in any case, one of the major factors here is excessive secretion of hydrochloric acid by the stomach in these individuals.

One of the techniques which has been in use for quite a number of years has been to subject these patients who have repeated difficulty with ulcers or who have gotten into trouble from severe hemorrhage or in rare instances from perforation of the ulcer right through the entire wall—one of the treatments has been to subject these patients to surgery and remove not the ulcer itself, but remove a considerable portion of the stomach and that portion in which lie the cells which produce hydrochloric acid.

Now, Dr. Wangensteen and his group at the University of Minnesota, within the past year, have come upon the idea of freezing the wall of the stomach where the acid-producing cells are located, and thereby destroying these cells and in effect bringing about a physiological gastrectomy. They do this by putting a tube down the patient's esophagus on the end of which is a balloon; and then connected to the balloon, coming back out is another tube—it is really a double-barrelled tube. They pass into one of the openings of the tube an alcoholic solution which is cooled to an extremely low temperature, below the freezing point of water. The solution passes down into the stomach, circulates within the balloon and comes back up the other side of the tube, and over a period of an hour or so, the freezing action takes place which kills the acid-producing cells.

These studies have been carried out to date in approximately 20 patients, I believe, and the end result of these studies is not clear. It will take much more work to evaluate the effect. There have been some mild recurrences to date, but the potential advantage of this form of treatment is that it could be repeated again in a medical form of treatment, rather than subjecting the patient to surgery. We are undertaking at the present time a cooperative study by a group of gastroenterologists, and also statisticians who are very familiar with medical problems, who plan to make a very objective evaluation of the effectiveness of this treatment.

Mr. FOGARTY. Is Dr. Wangensteen working under a grant from you people?

Dr. WHEDON. Yes, he is, Mr. Chairman.

Mr. FOGARTY. Is there anything else you want to mention?

Dr. WHEDON. I would be glad to continue.

NEW FASTER TEST FOR PRESENCE OF NARCOTICS AND BARBITURATES

I think one interesting development by investigators in our laboratories in Bethesda in the section on Medicinal Chemistry should be mentioned. This group, which was formerly headed by Dr. Nathan Eddy, who is an outstanding authority in the field of narcotics, and is now headed by Dr. Everett May, has developed an unusually sensitive and rapid method of detecting and identifying narcotics, barbiturates, and phenothiazines in the urine of patients.

This will be a very valuable tool in recovering for further treatment drug addicts who have relapsed. In the past, when drug addicts who

have relapsed have gotten into trouble and been picked up by the police, and the police have suspected them of addiction, in order to determine whether or not they have been taking narcotics, the urine has had to be subjected to a form of analysis which is very complex and took a great period of time, usually 2 or 3 days of continuous work.

Well, now, the technique which our investigators have worked out or rather have applied to this problem of testing for the presence of narcotics or barbiturates, is called thin layer chromatography. It has shortened the period of examination to a period of only 4 or 5 hours; and, in addition, this technique is many times more sensitive than the old fashioned technique that I was just describing that took several days.

Mr. LESINSKI. Of the skin?

Dr. WHEDON. This is an examination of the urine. It is a chemical technique that takes only 4 to 5 hours, so that if an addict is picked up, only a relatively short period of holding the addict will establish whether he has gone back to drugs. This same technique can be used for barbiturates and will be of help in speeding the diagnosis of the individual who has attempted suicide by taking excessive amounts of sleeping pills, because of the shorter period required to make a urinalysis of the presence of barbiturates.

BUDGETARY RESERVE

Mr. FOGARTY. Doctor, the 1963 appropriation, adjusted for comparability, is \$102,892,000 and the request for 1964 is \$114,717,000, an increase of \$11,825,000. However, there is a reserve of \$2,094,000 from 1963 funds so the estimated spending level provides for an increase of \$13,919,000. How much of the reserve is for forced savings?

Dr. WHEDON. \$94,000.

Mr. FOGARTY. What accounts for the remainder?

Dr. WHEDON. The remainder is split up as follows, as I remember: \$1,750,000 in research grants and \$250,000 in training grants.

HEMOPHILIA

Mr. FOGARTY. Last year we said in the report we would expect that research on hemophilia be strengthened. What have you done in this regard?

Dr. WHEDON. Mr. Chairman, we have made some definite headway in this area. I would like, if you are interested and will permit me, I would like to give a very brief background.

Mr. FOGARTY. Go ahead.

DESCRIPTION OF HEMOPHILIA

Dr. WHEDON. Hemophilia is the name given by physicians to a fairly specific clotting disorder in which a particular protein in the blood is missing or is present in less than normal amounts.

What I wish to get across, if I can, is the fact that there are many clotting disorders which are very closely related to hemophilia, and the individuals in various public organizations and societies who are interested in doing what they can to stimulate interest in these dis-

orders, recognize this; so even though there is an organization called the National Hemophilia Foundation, they do not limit their interest to hemophilia. They are interested in helping all they can the patients and families who have a variety of clotting disorders, generally centered around some particular defect in a protein of the blood that is related to the clotting mechanism.

Now, in order to have a normal clotting mechanism, there are three areas which must be maintained in a normal state by the individual. One is blood vessel wall integrity. Obviously, if the vessel is cut, the integrity is lost and bleeding occurs. But from a medical point of view, the disease of scurvy, in which there is an outstanding lack of vitamin C, is an example of a situation where you have weakness of blood vessel walls.

The second area that is important is that one must have an adequate number of blood platelets. These are tiny cellular substances which are actually somewhat smaller than the red blood cells and are essential for clotting. At the time that a cut or wound occurs, platelets secrete a substance which assists in the process of forming the end product of a clot, fibrin.

And the third area that is essential for normal clotting is the presence of normal amounts of a series of special protein substances—thromboplastin, prothrombin, fibrinogen—which sequentially go through chemical steps to result in the end protein, fibrin, which is the actual red thick clot that one sees when a cut stops bleeding in a natural fashion.

HEMOPHILIA RESEARCH FINDINGS

Now, hemophilia results from the lack of one of these special proteins—not the ones I mentioned, but a protein called antihemophilic globulin. In relation to this disorder, and, as I say, to very closely related coagulation disorders which are called hemophiloid diseases, Dr. Laki and his associates in our laboratory in collaboration with another physician with the name of Lorand, have found a new one of these protein substances that I have been describing, which for the moment is called the Laki-Lorand factor. The significance of this factor is that it is important for forming a stable, firm clot—you might say vulcanizing a clot into a hard rubbery mass which will really hold back the flow of blood in injured areas.

Dr. Lagi has also found that a chain of amino acids, known as Peptide B, is released during the clotting process, and they found that this peptide acts in two ways. It is part of this sequence of chemical steps which leads to formation of fibrin, but it also has a physiological action on the smooth muscle in the walls of the blood vessel which causes constriction or contraction of the blood vessels so that they clamp down in a situation where bleeding has occurred and will obviously lead to an improvement in the speed with which a clot takes place.

Mr. FOGARTY. Thank you, Doctor.

SKIN DISEASE RESEARCH

We also said we would expect more vigorous skin disease research programs.

Dr. WHEDON. Yes, sir.

Mr. FOGARTY. Mr. Denton asked a question the other day on what you are doing with regard to psoriasis.

Dr. WHEDON. I will be glad to speak to those questions, Mr. Chairman.

Dermatology—in the field of support of research activity in dermatology, during the past year we have increased our grants in this area by approximately 50 percent. Last year we, in cataloging our various grants, had 35 grants amounting to about \$700,000 and as of just the other day we were up to 50 awards, totaling slightly more than \$1 million, so that in this general field we have brought about an increase in our support of about 50 percent.

DEFINITION OF PSORIASIS

Now, with regard to psoriasis, the very interesting development here is that while we do not understand the cause of this condition in which there is an excessive piling up of the cellular layers of the skin, investigators have found that at least in part the difficulty is due to a greatly increased turnover or increased metabolism of the cells of the skin.

The cells of normal skin are replaced about once every 28 to 30 days. In other words, the cells in your skin present this day, 1 month from now will be completely replaced by brand new cells. Now, in the patient who has psoriasis, in the areas where he has psoriasis, the turnover is about seven times as rapid. In other words, from the time that a new cell develops in that area by division of a parent cell to the time when it dies is only 4 days, and this accounts for the tremendous buildup of the cellular layers, so that you have a horny, rough, and red area.

METHOTREXATE TREATMENT OF PSORIASIS

Investigators have thought that this might be attacked by applying, either locally or by mouth, some chemical substances which are called antimetabolites; that is, they attempt to suppress the rate of growth and speed of life, so to speak, of skin cells.

In collaborative studies between the rheumatic disease group in our Institute in Bethesda and the dermatology investigative group of the National Cancer Institute, also in the clinical center, patients with psoriasis and patients with psoriatic arthritis have been given methotrexate, which is one of the cellular poisons which is being used for various types of cancer. The interest in this study was not limited to the effect on psoriasis, but there was an interest also in the possibility of developing a new drug for the treatment of rheumatoid arthritis. It was observed that when patients were afflicted with either this unusual type of arthritis that we call psoriatic arthritis, and the slightly different situation where a patient may have straightforward rheumatoid arthritis and psoriasis—in both of these types of conditions, when the drug methotrexate was given, there was a very significant melting away of the psoriatic skin and also an improvement in their joint disease.

Mr. FOGARTY. Is this poisonous?

Dr. WHEDON. This is indeed poisonous, Mr. Fogarty, and you put your finger directly on a very significant problem in the possibility of using this drug as a widespread very effective treatment for either psoriasis or rheumatoid arthritis.

The compound is indeed very toxic and must be given in very limited and carefully controlled doses. To date, in some 30 patients which have been studied, to avoid serious untoward effects, physicians doing this work have had to be constantly on the alert.

There is another difficulty with this methotrexate treatment, and that is that after the compound has been given and a definite effect is brought about, if the treatment is stopped, both the arthritis and the psoriasis will come right back. Thus, once you start treatment, you have to continue it. The outlook here is a very interesting one—we have gotten a very good lead here on something to do—but we have either got to have our chemists come up with a related drug which will be definitely less toxic or else come up with some other substances which will be protective of the poisonous actions of methotrexate.

Mr. FOGARTY. You say they are using it in some cases of cancer?

Dr. WHEDON. They are using it in some cases of cancer. I am not familiar with the specific types.

Dr. SHANNON. One fairly dramatic effect is in cancer of the uterus—a test primarily in the cancer field—because methotrexate is the first chemical known to have produced a complete reversal of tumor growth.

GRANT PROGRAM LEVEL

Mr. FOGARTY. Most of your increase is in research grants, an increase of \$11,691,000. Again, Doctor, I do not say it is your fault, but this is just another leveling off of the program. This budget is geared to financing exactly the same number of new grants in 1964 as in 1963; is that right?

Dr. WHEDON. Actually, the number of new projects is slightly increased. I think for next year the suggested number is 368, and I believe for the preceding year it is in the range of 320.

Mr. FOGARTY. On page 16 of the justifications it looks the same to me. Under the "Decrease or increase" it says "zero" in my book.

Mr. KELLY. There is an increase of 368 grants. It is the same number of new grants, 732 in each year.

Dr. WHEDON. The point I would try to make with you, Mr. Chairman, is that whenever one awards a new grant, this is an extension of the program. This means that this is an increase in the activity in this area.

Mr. FOGARTY. When you have the same number of new grants in 1964 as in 1963, it does not look to me like you are progressing much.

Now, suppose that the 732 new grants in 1964 were cut down to 1 new grant. Would you give me the same answer that there is one new grant in 1964, so this is an increase in the program?

Dr. WHEDON. Well, that would be an increase of a considerably different magnitude, and it would be a very serious situation. That I would not like to see.

Mr. FOGARTY. Taking your logic, you could still say, "Well, there is one new grant in 1964, so that shows some increase in that area." Do you not expect more good worthwhile applications to be submitted next year than this year?

Dr. WHEDON. Yes, we do, Mr. Chairman.

During the past year we saw an influx of applications which led to an increase of our awards in research grants amounting to \$13 million. So that while I do not know what degree of business we will have coming in to us during the next year, I anticipate there will be business of the same order of magnitude and that we will be continuing to increase our awards in research grants.

COLLABORATIVE STUDIES

Mr. FOGARTY. What progress have you made in your collaborative studies?

Dr. WHEDON. Mr. Chairman, in collaborative studies we have two main activities: one, in epidemiology, which is housed in what we call our Epidemiology and Biometry Branch. The other activity is what we term our international nutrition studies.

EPIDEMIOLOGICAL STUDIES

In the epidemiological studies the workers in this Branch have been interested in various projects which attempt to work out the relationship between environmental and genetic factors to the incidence and the cause of various diseases.

As an example, one of these projects, is a study being done at the House of the Good Samaritan, a hospital in Boston, Mass., where the incidence of rheumatic fever among approximately 1,000 families is being investigated in comparison with the various blood groups or blood types which these families have. If it can be found, for example, that there is a predilection for recurrence of rheumatic fever in individuals who have a certain particular blood group or say, a small number of blood groups in comparison to the vast numbers we now recognize, these individuals would be selected out for particular attention as far as prophylactic antibiotic medication to try to prevent recurrence of attacks. Actually, in what these investigators are attempting to study—and these results are highly preliminary—we do not have the final word—it looks as though there is a closer relationship to so-called genetic factors which can be detected by examination of the individuals' saliva; as an example of this, there is a so-called taste test in which an individual is given a substance which to some individuals tastes extremely bitter but to other individuals who have a deficit of a particular gene, no taste is detected at all.

Then there are other projects in this area in which the principal investigator, again at Bethesda, is interested in various complex blood proteins such as transferring, which is important for the carriage or transport of iron in the blood, and the relationship between the presence or absence of this substance in various diseases.

INTERNATIONAL NUTRITION STUDIES

Mr. FOGARTY. Why are you cutting back from \$900,000 in 1963 to \$713,000 in 1964?

Dr. WHEDON. This change, Mr. Chairman, relates to a change in program activity with regard to our international nutrition studies. When the 1963 budget was prepared, we had in mind to bring to Bethesda a group which would intensify our efforts in international

nutrition studies, headed by a world renowned investigator. During this past year, however, this investigator and his group decided not to come to NIH and we find ourselves now in a situation where we have to reevaluate and reconsider at what level of activity we can pursue this work, and the results, Mr. Chairman, are that we will be pursuing our research in this area at exactly the same level as last year.

BASIC RESEARCH IN GENETICS

Mr. FOGARTY. You indicate on pages 21 and 22 that you are doing basic research in genetics; is that right?

Dr. WHEDON. That is correct.

Mr. FOGARTY. I thought that was done under general research and services. What is the difference between what they do and what you do?

Dr. WHEDON. The situation here is that we have a group of intramural investigators, that is, investigators in our laboratories in Bethesda who are very active in this work, whereas the Division of General Medical Sciences has no intramural laboratories and carries the major share of the support of work in this area by research grants to investigators outside.

Would you like me to say something about the progress we have made in this area?

Mr. FOGARTY. Yes.

Dr. WHEDON. Mr. Chairman, I hesitate to launch into a description of the chemical processes involved in the genetic code.

Mr. FOGARTY. I do not blame you. But if we are exposed to this enough, some of it may wear off on us. Go ahead.

Dr. WHEDON. I shall make the attempt in a modest way. You have heard of the substance called "DNA." This is a very complex protein which is located in the nucleus of all cells and is apparently the key substance which enables cells to transmit, from one generation to another, the same characteristics. It enables, further, an individual to transmit to his offspring the special characteristics of hair color, eye color, etc.; not only these obvious characteristics, but some other characteristics of the kind and nature of various proteins in the blood that I have referred to with regard to hemophilia, for example.

Now, in addition to DNA, which is the parent complex protein, there is another substance which has been shortened to the term "RNA." This is a messenger substance which carries the "orders from the front office," you might say, that is, from the nucleus of the cell, to the main body of the cell where various chemical activities go on, and the activity that has been under the greatest study has been the manufacture or the synthesis of various proteins.

From the nature and makeup of the substance called RNA, an appropriate message can be taken from the nucleus to the part of the cell which then undertakes the manufacture of a specific amino acid.

More specifically, they have found in analyzing the structure of RNA that there are four substances called chemical bases, whose arrangement and number actually are the code as to which amino acids shall be manufactured. In other words, if you have a combination of three bases all of the same type, plus one of the other type, you get, say,

phenylalanine synthesized in a predominant fashion, but if there are two of one base and two of another, as another type of a code, perhaps the amino acid valine will be produced.

Now, the work done on this, which was done originally by our laboratories in Bethesda, was with a test tube system based on a suspension of cellular material from bacteria. Thus, we knew then how bacterial cells were directed to produce various amino acids.

During the past year we have not only found that various virus cells have exactly the same code, but more recently Dr. Elizabeth Maxwell, in our laboratory of molecular biology, set up the same type of system using rat liver. Therefore, we now know that these mammalian cells use precisely the same system of transmission of genetic information that other types of cells do, so that in effect we are fairly certain that the genetic code is universal, that it applies to all forms of living cells.

This, we feel, is a major step in our understanding of how this code works and will lead to other developments which will be very important.

PROTEIN MAKEUP AND VALUE

Mr. FOGARTY. What is an amino acid? What part does it play?

Dr. WHEDON. Amino acids are the building blocks of protein. Various combinations of amino acids are put together to form larger groups called peptides or polypeptides, and then in turn various types of peptides and polypeptides are put together to form the protein that you find in meat, muscle.

Mr. FOGARTY. What is protein?

Dr. WHEDON. Protein is one of the three major constituents of tissue and has as its major elemental substance, nitrogen. Nitrogen is the element which distinguishes protein in its composition from fat and carbohydrate.

Protein is the essential substance in muscle tissue, but it is also found in other parts of the body—the skin and blood vessels and the organs, and has as one of its principal characteristics, contractility. We could not live without the ability to contract the muscle which is in your heart and mine. We could not move without the contractility of the muscles of our legs and arms.

The basic substance of muscle, through a variety of chemical reactions, permits contraction—that is protein.

Mr. LESINSKI. A body builder?

Dr. WHEDON. Yes, sir. We need it in our diets to replace each day, very nearly, the protein which is broken down in various chemical processes during contraction, also in the ordinary wear and tear of everyday living and also as a building block for the synthesis of new proteins for various purposes.

Mr. FOGARTY. Fats and carbohydrates, are they built along the same lines?

Dr. WHEDON. Yes; with respect to fats, the fats can be synthesized in the human body from carbohydrates, whereas the carbohydrates, that is, the sugars of one type or another, cannot be newly synthesized and have to be taken in, in the diet.

CYSTIC FIBROSIS

Mr. FOGARTY. What are you doing in cystic fibrosis?

Dr. WHEDON. In cystic fibrosis, again, Mr. Chairman, we have something which we can describe to you which I think will be of interest.

This disorder, as I think you and the committee are aware, has to date, been thought to involve principally relative young children. By virtue of metabolic defects which result in impaired secretions of the pancreas, particularly, and also of the lungs, there is impaired digestion, primarily of fats, so that the patient becomes, sometimes, severely malnourished: and also, because of the altered secretions in the lungs, which normally work to rid the lungs of the dust and germs which naturally go in and out of our lungs every day with every breath that we take—as a result of the impairment of the pulmonary secretions, they become thickened, the patient is unable to carry out this natural clearing function, and patients are very apt to develop a severe pneumonia which is very difficult to treat.

Investigators in our laboratories have been interested in expanding the use of various tests to detect patients with this disorder. It has been known that the clear cut, flagrant cases of cystic fibrosis have altered secretion of sweat by the skin, and the skin test of salt is the best known diagnostic test.

What has been found very recently, in fact, primarily during the past year, has been that individuals who are carriers of this genetically determined disease also have an abnormality of the sweat secretion.

If one were to examine the sweat from, say, the parents of patients with the flagrant disorder, or other individuals who carry this disease, but apparently do not have it, one finds that under normal circumstances, the salt concentration of the sweat is normal. When these individuals are subjected to the stress of heat, or given corticosteroid drugs, the salt concentration increases rapidly, far out of proportion to the normal response.

Now, what this means to us, is that there are considerable numbers of individuals in the population, whom we have heretofore described as only carriers of the disease, but who, probably, in reality, have a modified form of the disease. In other words, they have a slight case of cystic fibrosis, and would, under unusual situations, be subjected to some of the same problems of malnutrition, impaired absorption, and digestion of food stuffs, and to the occurrence of bronchial pneumonia. If we can identify these individuals by these new tests that have been worked out, then these individuals can be protected with respect to infections and can be given appropriate treatment to improve their digestion.

OSTEOARTHRITIS

Mr. FOGARTY. Osteoarthritis is worse than rheumatoidarthritis, is it not?

Dr. WHEDON. It is more prevalent than rheumatoidarthritis. It varies greatly in its severity, but it can be extremely crippling when it involves the joints of the hip or of the spine.

Mr. FOGARTY. It is a progressive thing, is it not?

Dr. WHEDON. It is a gradually progressive disorder. Rhenmatoid-arthritis generally progresses much more rapidly if it gets into a progressive state, but the osteoarthritis you have just described, can become extremely crippling and painful also.

Mr. FOGARTY. There is not much you can do about it?

Dr. WHEDON. At the present time, our major efforts with this disease are to diagnose it at a relatively early age and get the patient to a physician who will in turn prescribe what we call physical therapy. By appropriate attention to the function of the muscles and of the joints, so that the joints keep moving through their full range of motion, and with aspirin particularly, to relieve the pain, motion can be continued; then we can in a considerable measure, prevent the crippling aspect of osteoarthritis.

Mr. FOGARTY. That is, if you get them in time?

Dr. WHEDON. That is correct.

Mr. FOGARTY. Most people don't go to a doctor in time.

Dr. WHEDON. I think that is certainly an important part of the problem.

Mr. FOGARTY. Is there anything else you would like to say, other than what you talked about?

DIAGNOSIS OF DISEASES OF LARGE BOWEL

Dr. WHEDON. Mr. Chairman, we have another interesting development here, which is in the line of considerable improvement in our armamentarium for diagnosis of diseases of the large bowel.

Investigators sponsored by our Institute at Washington University in St. Louis, have come up with the new technique of administering an enema which consists of a whitish solution which, once introduced into the bowel, forms a jellylike substance. It is called a silicone foam, or silicone mold, method of diagnosis for disorders of the lower bowel.

The rubbery mold which forms inside the bowel is extremely soft so that it is very simple for the patient to expel it. Then the mold can be washed and carefully examined, and the mold will show fairly clearly if there are indentations made in the mold, because of an outgrowth in the wall of the large bowel. It will also show very clearly if there is a constricting portion, if there has been a growth outside of the bowel which is forming a tight ring, so that the passage of material through the bowel is going to be obstructed. This is often a telltale sign that there may be cancer, growing about the bowel.

Not only will this mold show the physical abnormalities of some disease of this type in the bowel but if the mold is treated very carefully, the washings can be examined for cells which have been picked up from the lining of the bowel and examined by the papanicolau stain that you are familiar with for the presence of cancer cells.

Mr. FOGARTY. Does this eliminate the necessity of the proctoscope examination?

Dr. WHEDON. No, sir. I do not think so. It is really a distinct addition to our armamentarium for diagnosis.

We feel that direct examination through a scope is very important to the length of bowel that can be examined.

The sigmoidoscope is an instrument which will go in only approximately 15 inches, and for the higher segments of the bowel, one must

depend upon the X-ray examination from radio-opaque substances like barium. Hopefully, this new technique I have just described will add a significant factor to our ability to diagnose these diseases.

Mr. FOGARTY. I see.

Mr. LESINSKI. How about piles?

Dr. WHEDON. Piles occur at——

Mr. LESINSKI. The lower end.

Dr. WHEDON. At the very lower end, and can be readily viewed with a proctoscope, which is very short.

Mr. LESINSKI. What about this mold?

Dr. WHEDON. This mold would not really be necessary for the diagnosis of piles, or hemorrhoids.

Mr. LESINSKI. But it would show up if you used the mold?

Dr. WHEDON. Yes; it would.

STUDIES OF POPULATION GROUPS

Mr. FOGARTY. What about your population studies?

Dr. WHEDON. Some years ago we initiated a study of a group of patients at Framingham, Mass., who have been under study for quite a number of years, by the Heart Institute, with respect to problems in their area of interest. This group is now being studied for the incidence of rheumatoid arthritis in the population. In addition to that, members of our rheumatic diseases group have undertaken a study of the Blackfeet Indians in Montana for the incidence of rheumatoid arthritis there, with particular interest in determining the significance of environmental versus genetic factors in this disease.

Thus far, the study among the Blackfeet appears to indicate that there is among this group not the particularly high familial incidence of the presence of the rheumatoid factor which has been found in previous studies, and the environmental influences may be greater. But what I wish to come to, Mr. Chairman, is to indicate that this study among the Blackfeet in conjunction with a study which is just getting underway at the present time, among a group of Indians in the southwestern part of the United States, plus other studies, will, we think, within the next year, bring forth the first truly sound incidence figures for rheumatoid arthritis.

TRAINING FOR ORTHOPEDICS

Mr. FOGARTY. Tell us what you are doing in orthopedics.

Dr. WHEDON. Orthopedics is an area which we have recently become particularly interested in. As I indicated earlier, Mr. Chairman, in talking about training, the stage where we are now, with regard to orthopedics, is to initiate interest in training among those few departments of surgery which are competent to train young surgeons who are interested in this field. Within a matter of years, these young trained individuals will reach the point where they can become independent investigators and then will begin to apply for substantial numbers of research grants. At the present time, our activities in research grant support in this field is not large.

LEVEL OF NIH BUDGET

Mr. FOGARTY. I think that completes my questions.

I just want to make the statement that the budget of the NIH is the most conservative budget that we have had. With the exception of the Mental Health Institute, there is no increase in the number of new research projects over the 1963 level. I am very much disappointed in that rate of progress.

In addition, some of the programs are actually cut back in 1964. It disappoints me greatly. I think it is one of the most conservative budgets which was ever considered by this committee.

Mr. Denton.

RELATIONSHIP OF ARTHRITIS AND METABOLIC DISEASES

Mr. DENTON. I never could understand why you had the arthritis and the metabolic diseases in the same institute. Is there any connection between the two of them?

Dr. WHEDON. Mr. Denton, this question is frequently asked of us. I think the best answer here is that when the Institute was formed by an act of Congress in 1950, as were several other institutes at about the same time, a logical grouping was sought for various interests and activities related to the various diseases, and 1950 followed by only 2 year the discovery of cortisone, which is a steroid hormone of the adrenal gland, which, you see, is in the realm of endocrinology and metabolism, and cortisone was, at that time, the striking new development in the treatment of rheumatoid arthritis and of course, with reservations, still has a very active role in the treatment of rheumatoid arthritis. We had, at least through this development, an instance of the very close link between arthritis problems and the problems of endocrinology and metabolism.

Mr. DENTON. That is all I have.

Mr. FOGARTY. Mr. Lesinski.

TRANSMISSION OF HEMOPHILIA

Mr. LESINSKI. Dr. Whedon, it is an old English theory that the sins of the grandparents fall upon the grandchild, and I don't know how true that is, but you mentioned the fact that it is hereditary and whether it is the grandparents that bring it about, I do not know, but that is the old school of thought.

You mentioned hemophilia. Did not the Hapsburgs of Europe have that disease, especially in Spain?

Dr. WHEDON. That is correct.

Mr. LESINSKI. You mentioned the fact that it is transmitted by the father.

Dr. WHEDON. It is transmitted through the female side of the family to the males. The males are the ones who have the disease, but it is the female in the family who transmits it.

Mr. LESINSKI. I am glad you clarified that because I was going to hop on you at that point. It was brought to the Romanoffs through marriage in the—I believe it was one of the northern royalty and from there, was transmitted to the other royalty of Europe.

You are quite correct about the females. It is transmitted by the females, and the males are the ones who suffer by it.

SWEAT PRODUCING SUBSTANCE

When you mentioned cystic fibrosis, you mentioned a chemical that reacts on your sweat glands when you perspire.

Dr. WHEDON. There is a chemical (pilocarpine, placed on the skin) which is used in the cystic fibrosis test to increase the outpouring of sweat so that the sweat may be examined.

Mr. LESINSKI. Would you do me a favor and yourself a favor, and try vinegar instead?

Dr. WHEDON. Try what?

Mr. LESINSKI. Vinegar. Vinegar has the ability to bring out perspiration.

A month from now, 2 months from now, a year from now, I would like to know what the result is.

Dr. WHEDON. I would be glad to do that, Mr. Lesinski, but the point of increasing the sweat is not with regard to any therapy but with regard to a means of making the sweat readily available for examination.

Mr. LESINSKI. That is the point. That is true. Would you make that one experiment to see what the answer is, if you don't mind?

Dr. WHEDON. Internally?

Mr. LESINSKI. Internally.

Mr. FOGARTY. Does it make you perspire more?

Mr. LESINSKI. This is off the record.

(Discussion was had off the record.)

Mr. LESINSKI. Mr. Rayburn believed in the use of honey, quite extensively, instead of sugar.

LABORATORY TESTS ON HUMAN HAIR IN POISON CASES

I don't know the exact poison that was used, whether it was cyanide or just what, now, but it is claimed by some that the death of Napoleon was not by normal cause, but by poisoning, and your dissertation brings this up to me, that they had found, recently, some of the hair, supposedly of Napoleon, they found extremely large amounts of cyanide in the lower part of the hair, which showed that he had received larger doses of poisoning than it would be possible for an average person to absorb. In other words, it had been for a long period of time that his system had been poisoned.

This is something that you are touching on. In other words, how the body reacts to poisoning. You clip off a piece and find out from that observation, what is in the skin, or whatever it may be.

Am I giving you a similar comparison?

Dr. WHEDON. Yes. Actually, what I was particularly describing with regard to the molecular disease, histidinemia, related to a technique for obtaining tissue to determine the presence or the absence of an enzyme.

Mr. LESINSKI. The hair is part of the skin of your body.

Dr. WHEDON. That is correct.

Mr. LESINSKI. Anything, therefore, that is thrown out of the skin goes into the hair.

Dr. WHEDON. The hair and skin have been examined by toxicologists for the presence of various poisons, particularly of course, when the subject under examination is no longer living.

The simplest biological substance to use, of course, is urine or blood, but in many instances, as you described, hair and skin have been examined.

USE OF GOLD IN TREATMENT OF ARTHRITIS

Mr. LESINSKI. One of the ancient remedies for certain types of disease was gold. I see you have an item in your budget here for gold, too. What is it? You are using a gold compound as a remedy for arthritis. That is as old as ancient Greece.

Dr. WHEDON. Yes, sir; gold is one of the forms of therapy of rheumatoid arthritis. There is, at the present time, a recommendation which is followed by most physicians who are experts in this field, that when a patient with rheumatoid arthritis is diagnosed initially, treatment is given which consists of aspirin and physical therapy. This form of treatment is effective in handling most of the levels of severity of rheumatoid arthritis that come to a physician, but if the disorder is more severe, then gold is recommended for extensive trial over a period of months. If this is relatively ineffective, then corticosteroid treatment is often given.

TRANSFER OF FUNDS TO MANAGEMENT FUND

Mr. LESINSKI. I noticed in your breakdown here, you have, on page 21, National Institutes of Health, you have \$4,441,000 to transfer to the National Institutes of Health management fund, for the 1964 budget.

Mr. KELLY. I wonder if I might explain that, Mr. Lesinski.

The way the National Institutes of Health are organized, is by categorical institutes, and the appropriations are made for them; but in order to get the highest degree of efficiency in the operation of the National Institutes of Health, they have centralized the services for research services, including the operation of the clinical center, the services for the review and approval of research and training grants, the operation of the ground and physical facilities in Bethesda, and the operation of the Director's office. Each of the Institutes contribute to this centralized operation. They are reflected in the budget under the title, "Payments to the National Institutes of Health Management Fund," and then in the justification, they are separately presented, the purposes for which these funds will be applied; how they are used; and why they are needed.

Mr. LESINSKI. I have no more questions, Mr. Chairman. That is all.

Mr. FOGARTY. Is there anything more you want to say, Doctor?

SPECIAL REPORTS ON CYSTIC FIBROSIS AND GASTROENTEROLOGY

Dr. WHEDON. Mr. Chairman, merely that I appreciate having had the opportunity to appear before you and to describe our progress and to tell you that we have prepared two special reports. One is on gastroenterology, and the other on our progress on cystic fibrosis, which we shall be glad to submit.

Mr. FOGARTY. We will put them and your statements on cost and research highlights in the record at this time.

Thank you very much, Doctor.

(The reports follow:)

SPECIAL REPORT: CYSTIC FIBROSIS

Cystic fibrosis has the highest incidence and mortality rate of any of the hereditary diseases of children. As a killer of children under 15 years it outranks even poliomyelitis, rheumatic fever, and diabetes. Although cystic fibrosis has been recognized as a specific disease only since 1938, its increasing frequency throughout the world has made it a public health problem of no mean proportions; estimates of its incidence in the population range as high as 1 in 1,000 live births. During the past 6 years, 25 State departments of health have included cystic fibrosis in their crippled children's programs because of the very heavy expense for necessary and continuous care which families of afflicted children must meet.

Cystic fibrosis (CF) affects the exocrine, or externally secreting, glands of children, adolescents, and young adults. These glands discharge their secretions onto the skin (sweat glands), or into organs connected to the body's exterior (lungs, intestines, etc.), either directly or through special ducts. In CF, the mucus producing glands do not secrete their normal, clear, free-flowing fluid. Instead they produce a thick, viscous mucus which tends to obstruct the ducts or openings of the glands. The thick mucus accumulates in various organs of the body and interferes with normal functions such as breathing and digestion.

Nonmucus producing glands—the sweat, salivary, and tear glands—are also involved. In fibrocystic patients, the secretions of these glands usually contain an excessive amount of salt, and, as a result, many patients are unable to conserve salt. In times of stress, during excessive sweating in hot weather for example, salt losses may be severe enough to cause death.

Nearly all CF patients develop chronic lung disease at some time during their illness. Thick mucus deposits clog passages in the lungs or the branches of the windpipe, causing labored breathing or chronic cough. In time, bacteria may multiply in the accumulated secretions, and the child may fall victim to chronic bronchitis. CF patients are extremely susceptible to lung infections and may succumb to pneumonia; lung disease accounts for 90 percent of the deaths from this so frequently fatal disease. Obstructed, damaged lung tissue may also impede blood circulation, and occasionally a child may die of chronic heart strain.

Cystic fibrosis is not an infectious condition acquired from others or transmitted contagiously. The disease is the result of an inborn error of metabolism, inherited from parents who carry the genetic trait for the disorder. A carrier of the trait may not show any symptoms of the disease, yet is capable of passing the trait to his offspring, who, in turn, may partially manifest the disease. When both parents are carriers, offspring have a chance of being born with cystic fibrosis.

Recent statistics show that among children in the United States, cystic fibrosis accounts for virtually all cases of pancreatic deficiency; for a great majority of chronic, nontuberculous lung conditions; and for much liver damage. Although thought of primarily as a disease of young children, improved diagnostic methods evidence an increasing frequency of cystic fibrosis among older adolescents; also, there is reason to believe that some adults with chronic lung disease may belong in the cystic fibrosis disease category.

In the past, both the National Institute of Arthritis and Metabolic Diseases (NIAMD) and the National Institute of Allergy and Infectious Diseases (NIAID) have conducted and supported fibrocystic research, the latter Institute primarily because of the close association of CF and infectious pulmonary disease. This year, for reasons of efficiency and economy, the cystic fibrosis program has been consolidated within the NIAMD. The consolidation will be complete at the end of the fiscal year 1963 when the NIAID's obligations to its CF grantees have been discharged.

PROGRESS IN CYSTIC FIBROSIS RESEARCH

Twenty-five years ago, when cystic fibrosis was first recognized as a specific disease entity, it was thought that pancreatic insufficiency was the basic defect responsible for the condition and the name given to it, based on microscopic examination of this organ, was "cystic fibrosis of the pancreas." This term was

misleading, however, for it is now known that the disorder involves many other organs and tissues, particularly the lungs, paranasal sinuses, sweat glands, liver, and rectum. The basic defect underlying cystic fibrosis is as yet unknown and much of the research carried on by Institute scientists in Bethesda and in the more than 30 active research projects supported by Institute grants is devoted to discovering its nature.

Scientists at NIAMD's Pediatric Metabolism Branch are making an effort to clarify the basic defect through the coordinated use of immunological and biochemical methods. In the first phase of this investigation, immunological screening techniques are employed to seek the location of an abnormal constituent common to all organs and tissues in fibrocystic patients. In the study's second phase, samples of body fluids and organ substances are subjected to chemical separation and purification by a variety of methods. Highly purified molecules isolated in this manner will be chemically analyzed to obtain information about the changes in structure and composition of mucoproteins (imperfectly understood proteins found in mucus) secreted by exocrine glands. This study represents the first comprehensive approach to the problem of the basic defect in fibrocystic disease.

Important advances in cystic fibrosis research have been made through the study of sweat. NIAMD scientists have developed an instrument to measure, simultaneously, the rate of sweating and the amount of salt in sweat. The instrument has provided some interesting and potentially important information on the deranged mechanism of sweating in the fibrocystic patient: Preliminary data obtained in a group of CF patients suggest that the relative inability of sweat glands tubules to reabsorb and return to the body a significant proportion of salt mobilized in the interior of the sweat gland, before it appears on the skin, is not due to a defect in the tubules themselves but to the formation of an abnormally concentrated precursor solution released originally in the acinar or "root" portion of the gland. Discovery of the exact defect in this mechanism might reveal a common denominator for the many apparently unrelated manifestations of cystic fibrosis in various organs of the body.

A particularly significant NIAMD finding was the discovery for the first time of mucoproteins in human sweat. This study also disclosed that CF patients had an abnormal concentration of the sugar fucose in their sweat mucoproteins, similar to the high concentration of fucose found by other investigators in previous studies of mucoproteins contained in fluid from the small intestines of CF patients.

Although the diagnostic value of sweat mucoprotein studies is as yet undetermined, they may be of great value to genetic research on CF as a reliable test to detect carriers, which has been lacking. The desirability of a test from the diagnostic, and especially the genetic standpoint, can be readily understood when it is realized that from 2 to 5 percent of the general population are thought to inherit the cystic fibrosis gene from one parent, and some adult patients with chronic lung disease and intestinal disorders of unknown origin have been thought to be heterozygous CF carriers in whom only a portion of the inherited trait for CF has become clinically manifest. Future studies with parents and blood relatives of CF patients will determine the responsibility of the mucoprotein work to genetic problems. These investigations will add not only to our knowledge of cystic fibrosis, but also sweat gland physiology about which little is known.

NIAMD grantees provided further understanding of the disease with the discovery in CF children of a previously unknown deficiency of a fat-splitting enzyme, lipoprotein lipase, normally active in the circulation. Since it was known that the failure of CF patients to absorb ingested fats from the intestine is due to a deficiency of pancreatic lipase, the investigators have suggested that their finding may be explained on one of two bases: either the lipase deficiency in CF is more widespread than hitherto believed and involves organs in addition to the pancreas, resulting in a generalized deficiency of more than one lipase; or, poor intestinal absorption of triglycerides over a long period results in lack of stimulation and mobilization of lipoprotein lipase within the circulation.

While these investigations of the basic mechanisms of cystic fibrosis are laying a foundation for future practical advances, work along clinical lines has improved the day-to-day therapeutic management of CF patients. During the past year, over 100 patients have been studied and treated by NIAMD's Pediatric Metabolism Branch. About half of these were hospitalized while the remainder were treated as outpatients.

The search for therapeutic agents effective against the chronic pulmonary disease that causes the death of most CF patients continues with trials of the newer antibiotic and mucolytic agents, some of which appear promising. Special attention is being given to a change in the respiratory flora, from the commonly found *Staphylococcus aureus* to the difficult-to-treat *Pseudomonas aeruginosa*, following the use of effective anti-staphylococcal agents.

The incidence and pathogenesis of the failure of vision which occurs in CF is under study in collaboration with the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness. Some of these complications may be due to long term toxicity of therapeutic agents. If this is true, it will result in drastic changes in treatment and have important practical implications.

Measles is a severe and sometimes fatal complication of CF. In an effort to protect CF patients, the advisability of giving them live measles virus vaccine was tested earlier by NIAMD clinicians, in cooperation with the Division of Biologics Standards, and more recently by grantees of the National Institute of Allergy and Infectious Diseases. The reactions in most CF patients tested were acceptable, but the degree of protection conferred remains to be precisely determined.

These and other developments in diagnosis and therapy are being transmitted promptly to practicing physicians and research workers throughout the country. One particularly effective means of communication has been a comprehensive scientific exhibit on cystic fibrosis specially prepared by the NIAMD. This exhibit, along with detailed, practical literature concerning the most recent and effective forms of diagnosis and therapy, has been brought to the attention of thousands of physicians at medical meetings and conferences all over the United States.

An important adjunct to laboratory research in cystic fibrosis is a pilot survey financed by a research contract from the National Institute of Allergy and Infectious Diseases and conducted by the Children's Bureau with the cooperation of the National Center for Health Statistics. This survey is designed to provide an index to the size of the CF problem on which to project future research efforts.

In the area surveyed, Massachusetts, New Hampshire, and Vermont, a total of 621 patients with cystic fibrosis received medical care at some time during the 8-year period of 1952 through 1959. The annual number of recognized cases increased about 57 percent, essentially because of improved diagnostic procedures. The annual case load of the disease, among children under 18 years of age, rose from about 12 per 100,000 population in 1952 to 22 per 100,000 population in 1958. During a 7-year period, the number of patients with cystic fibrosis doubled in the age group under 5, tripled in the age group 5-9 years, and quadrupled in the group 10 years and older.

The figures are encouraging inasmuch as they show that early diagnosis and improved treatment are allowing children with cystic fibrosis to live far longer than in the past. A preliminary rough estimate of the incidence of diagnosed cases in the pilot area is only 42 per 100,000 live births or 1 per 2,300 live births. Although this is a lower estimate than that usually given for the population in general, it excludes stillborn babies and diagnosed cases in newborns who died before leaving the hospital, and only counts patients under the medical supervision of either the pediatrician or clinic contacted by the survey.

The genetic character of CF makes the disease particularly pernicious. As advances in therapy make it possible for fibrocystic patients to reach the reproductive age, the "load" of CF traits in the genetic pool of the population will increase. If the basic genetic defect in cystic fibrosis and a method of correcting it permanently are not discovered, an ever-increasing sector of the population may find itself heir to the gene. It is this characteristic which makes effective research on cystic fibrosis an obligation to future generations.

SPECIAL REPORT: GASTROENTEROLOGY

Disorders of the gastrointestinal system, which may range from stomach upset to peptic ulcer and ulcerative colitis, are among the most frequent ills to which man is heir. Aided by support from the National Institute of Arthritis and Metabolic Diseases, however, the momentum of gastroenterological research has been increased by the growth of biochemistry, development of new

technics and the expanding availability of new mechanical and electronic devices. Since progress in research in this field is inseparable from clinical advances, large numbers of patients who suffer from peptic ulcers, inflammatory enteritis, biliary colic, cirrhosis, pancreatitis, or even simple constipation, among other disorders, have benefited.

The fusion of technics and thinking of biochemists and clinicians has resulted in new approaches to the problems of gastroenterology. Scientists, for example, are applying their new knowledge to studies of infinitesimal metabolic processes that take place in the cells lining the stomach, intestines and gall bladder so that these processes can be related to gross physiological activity.

MALABSORPTION STUDIES

In the past year, both the clinical and laboratory research activities of the gastroenterology unit of NIAMD have been concerned with problems related to intestinal absorption. A major portion of the clinical activities has been focused on Whipple's disease, a poorly understood, grave disorder characterized by a defect in intestinal absorption of fat.

NIAMD scientists have demonstrated in four patients that relapses of this disease can be reversed rapidly and successfully by treatment with adrenocorticosteroid drugs used concurrently with broad-spectrum antibiotics. A fifth patient, treated with antibiotics only, also improved, but at a much slower rate.

Institute scientists, in collaboration with investigators from the National Cancer Institute, have also clarified the nature of hypoalbuminemia, an abnormally low content of the protein albumin in blood, which accompanies Whipple's disease. By intravenously injecting albumin labeled with radioactive chromium, it was determined that the hypoalbuminemia is largely due to excessive protein loss in the gastrointestinal tract. (Since chromium is not absorbed by the intestine, the amount of radiochromium which appears in the feces is an index of the amount of albumin which leaked into the intestine from the circulation.)

Good progress has also been made in basic research studies involving intestinal absorption. It is common clinical practice to assess intestinal absorption in patients by feeding them 25 grams of d-xylose and measuring the urinary excretion of this carbohydrate. Little is known, however, about the pathways of metabolism of d-xylose in mammalian tissue, and less is known about factors other than intestinal absorption which may influence the results of this xylose tolerance test. A study to delineate the pathways of liver metabolism of d-xylose has already resulted in the purification of an enzyme actively involved in the breakdown of that carbohydrate.

Because information on amino acid absorption in the healthy and diseased human subject is limited, the NIAMD scientists are studying this physiologic process. In the past year, the first phase of the study has consisted of an evaluation of active transport of certain amino acids across the intestinal mucosa in segments of hamster small intestine. Information so derived will now be applied to human subjects.

There has also been a steady accumulation of knowledge resulting from the investigation of glucose metabolism in the mucosa of the small intestine. NIAMD scientists have prepared extracts of animal and human intestinal tissues to see what effect hydrocortisone, a steroid hormone, has on glucose metabolism. The small intestine allegedly derives much of its energy for active transport of nutrients from the intestinal lumen into the circulation from glucose oxidation; hence an understanding of this biochemical pathway is important in relation to probing mechanisms of the intestine's functions.

OTHER MALABSORPTION STUDIES

Surgery has played an outstanding role in the development of gastroenterology as a special field of research and clinical practice. The Institute supports a great many surgical investigators who have contributed numerous new ideas. For example, last year Institute grantees at Jefferson Medical College in Philadelphia did not believe there was adequate explanation for the impaired absorption of fats seen in about 50 percent of ulcer patients who have had a large portion of their stomachs removed (Billroth II operation). They undertook a study and found that the fluid taken from intestinal loops bypassed by the operation exhibited high bacterial counts, thus strongly suggesting that excessive bacterial growth in these surgically created stagnant, dead-end loops interferes with fat absorption.

Other surgeon-grantees at the Loma Linda University School of Medicine in Los Angeles have reported an unusual, dramatic method to manage the problem of malabsorption following massive intestinal resection. Extensive resections of the small intestine are most frequently performed for major gangrenous involvement of the intestine following vascular occlusion or volvulus (intestinal "twisting"). When more than 200 centimeters, or approximately 7 feet of the small intestine is removed, the resection is generally considered to be massive, and the immediate mortality is high. The majority of those who survive develop an often fatal, short-bowel syndrome with clinical features of malabsorption, such as diarrhea, inability to digest fats, severe weight loss, and anemia.

Earlier investigators showed that long-term survival was possible in the dog when a reversed 3 to 5 centimeter segment was interposed in the continuity of the intestinal tract. In this short segment the direction of the intestinal waves of contraction, and thus of the motion of the intestinal contents, is reversed. This results in the local introduction of a brief "upstream" mobility into the generalized "downstream" trend, delaying the total transit time of vital food material and promoting increased absorption. The NIAMD grantees successfully carried out the "surgical reversal" method in the case of an 84-year-old patient, and demonstrated the feasibility of the method for further trials.

The active support extended by NIAMD to the field of gastroenterology has helped bring about this field's dynamic transition from the mild interest of a few years ago to today's renewed excitement. This is borne out by the important roles played by NIAMD-supported scientists and intramural investigators in developing exciting new methods and ideas since the Institute was created. Some of the most dramatic and significant studies in gastroenterology have been reported in the past 12 months by scientists supported by the Institute.

NEW PEPTIC ULCER TREATMENT

Duodenal ulcer is a common disease, but its cause is not fully known. A significant percentage of productive segments of the population are affected by this disease, and economic repercussions are felt during the long periods of rest required for the medically treated patient, or during convalescence of a patient after surgery.

In preliminary studies of an unusual therapeutic technique during the past year, NIAMD grantees at the University of Minnesota Medical School have been able to produce healing of duodenal ulcers in 35 patients by a method of freezing the acid-producing mucosal lining of the stomach for short periods of time. The technique, which involves perfusion of frigid liquid through a balloon placed in the patient's stomach, has resulted in "physiological gastrectomy" without physical loss of the stomach, and symptoms and signs of duodenal ulcers have disappeared after treatment.

It is too early to determine whether permanent healing results, but discussions are underway to determine the feasibility of a multiclinic study of both the safety and effectiveness of this technique. Since it can be repeated if symptoms recur, it is possible that this new procedure will generally avoid the need for surgery by gastrectomy in many duodenal ulcers.

TECHNOLOGICAL ADVANCES

The recent availability of new electronic and mechanical devices has enabled biomedical researchers to make new advances in gastroenterology. One promising example is diagnostic findings, last year, by an NIAMD grantee at the University of Alabama Medical School, using his newly developed endoscope which employs a revolutionary, flexible optical system.

The new flexible instrument, called the "fiberscope," is used to examine areas previously inaccessible by endoscopy, and thus far has provided observations which may aid in the recognition and therapy of ulcers and other disorders of the upper gastrointestinal tract. It is completely flexible throughout its entire length, permitting easy passage and patient comfort. The fiberscope has high light transmission and good contrast even when the instrument is acutely curved, allowing still and motion pictures to be taken in color.

The new device has provided several observations which may aid diagnosis and therapy of ulcers and other stomach disorders; when used along with X-rays on more than 550 patients with various gastric and duodenal disorders, it was found to provide the correct diagnoses in 90 percent of the cases, many of which were otherwise unsuspected. Of particular interest was the frequent finding of

post-gastrectomy lesions, the majority undiagnosed radiologically and often clinically unsuspected. The grantee is presently improving the fiberscope further, and developing a similar instrument for pediatric use and a flexible fiber esophagoscope based on the same principle.

DIAGNOSTIC SILICONE FOAM MOLD

Beyond the reach of the sigmoidoscope, lesions of the colon often lie undetected, or, at best, difficult to diagnose. Although various attempts to solve this problem have been effective in spotting *large* lesions, they are frequently unreliable when it comes to small abnormalities. One possible solution came last year from NIAMD grantees at the Washington University School of Medicine who have developed a remarkably reliable method for detecting or clarifying the character of sigmoid colon and rectal lesions which are either imperfectly recognized or totally undiscerned by diagnostic X-ray examination.

The technique consists of a silicone foam enema which, once in place, jells in the colon to form a mold, taking on the contours of the bowel and reproducing an accurate, detailed imprint of the mucosal lining. Since the mold has a soft foamy consistency, it is evacuated spontaneously, usually within 15 minutes of administration of the enema, even through constricting lesions. Irregularities of the colon are clearly revealed on the mold surface, and any cells sticking to its surface can be washed off and examined microscopically to determine whether they are of malignant origin.

More than 80 persons, ranging in age from six to 81 years have been examined with the technique and have shown various colonic abnormalities, including polyps, adenocarcinoma, ulcerative colitis, and diverticula. (Since the NIAMD grantees at this stage of their experience with the technique have been primarily concerned with evaluating its efficacy and safety, many of their patients had colonic lesions which could be, and were, diagnosed by existing methods.) The NIAMD-supported investigators are now attempting to eliminate air-pocket artifacts and to develop methods to use this practical adjunct to clinical diagnosis elsewhere in the gastrointestinal tract.

ULCERATIVE COLITIS

Ulcerative colitis, unfortunately, still remains the outstanding unsolved problem of the large intestine, but investigators are providing new research approaches to determine the mechanism of this disease. In the past year, NIAMD grantees at the Yale University School of Medicine studying sera from 24 patients with ulcerative colitis have found that 18 of them (75 percent) exhibited circulating "antinuclear globulins", protein fractions which react specifically with nuclei from white blood cells, similar to the way in which other antibodies react with their type-specific antigens. Although it is not known what role the globulins play in ulcerative colitis, their presence offers further evidence for an altered immunological state in this disease.

Many previous studies have supported the thesis that hypersensitivity factors are involved in the etiology of ulcerative colitis. The fact that many such patients sensitive to drugs and blood transfusions, are benefited by ACTH and corticosteroid drugs, and often have concurrent disorders such as leupopenia, hemolytic anemia and rheumatoid arthritis, suggests the existence of an altered immune state in ulcerative colitis.

HEARTBURN

One of the most common, distressing symptoms experienced by man is heartburn. Some of the hypotheses advanced to explain its development include disordered motor function of the stomach or esophagus, oversecretion of hydrochloric acid, and a backflow of gastric contents into the esophagus. A number of difficulties, however, have hindered the proper assessment of these factors. In order to clarify symptomatic heartburn, Institute grantees at Los Angeles developed apparatus to measure both pressure (which may produce distention or enlargement of the esophagus, previously thought to be the cause of heartburn) and pH (degree of acidity) within the esophagus. By studying 12 patients with complaints of heartburn, they found that the symptom occurred when acidity was high in the esophagus and disappeared when the acidity decreased in the esophagus, regardless of the concomitant pressures.

Other studies conducted by NIAMD grantees have further clarified some of the basic mechanisms of the pancreas, liver and intestines. In the latter case, a preliminary study by an NIAMD grantee at the University of North Dakota School of Medicine has shown that one of the B₆ vitamins, pyridoxal-5-phosphate, is essential for the active absorption of at least two amino acids in the intact animal. The study has suggested that one aspect of clinical vitamin B₆ deficiency might be inability to absorb amino acids from the intestine. (Vitamin B₆ has been known to play some role in the active process of cellular uptake of amino acids, but it had not been apparent before the NIAMD-supported study that amino acid absorption in the upper small intestine of the living animal is an active process dependent upon at least one of the B₆-vitamin factors.)

Other grantees at the New York University School of Medicine during the past year have added significantly to fundamental knowledge of basic physiology of the pancreas and liver by accurately measuring pancreatic and biliary secretions in humans. The grantees have found that 24-hour bile output of apparently normal human lives varies between 1,000 and 2,000 milliliters per day, a quantity much higher than the value of 500 milliliters usually stated in textbooks. By using a new technique for collection and measurement of biliary-pancreatic secretions, the investigators also found that daily normal pancreatic secretions amount to 1,500 to 3,000 milliliters and occasionally as much as 4,000 milliliters. These amounts likewise are far greater than the 700 milliliters quoted in the literature.

The study also contributed extensive fundamental information on the normal daily output of bile salts and pancreatic enzymes and the effects thereon of food, hydrochloric acid, and anticholinergic drugs—all normal physiologic data not previously available.

RESEARCH IN GASTROENTEROLOGY

During the past 10 years, research in gastroenterology has revolutionized concepts and practices in the field, but gastroenterology still encompasses a great number of serious unsolved etiological problems. Certainly, problems of the gastrointestinal tract are not only numerous, they are also highly varied, ranging from disorders of the stomach and intestines, to diseases involving the liver, gall-bladder, bile ducts, pancreas, and peritoneum. Some of the basic mechanisms of these diseases have been clarified; many still elude medical researchers.

The blending of accepted methods of biomedical research with novel technological approaches has resulted in the development of new improved methods and techniques of diagnosis and therapy of gastrointestinal diseases. Laboratory research in gastroenterology no longer lags behind its true role in clinical practice, largely because of the catalytic role played by the programs of the National Institute of Arthritis and Metabolic Diseases. There still exists an urgent need for the infusion of additional research workers into the field, a need which the NIAMD will endeavor to fulfill through its continued support of research and research training in centers across the country.

DEATHS, DISABILITIES, AND COST OF ARTHRITIS AND METABOLIC DISEASES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

Arthritis and metabolic disease activities

Statistics concerning the annual number of deaths and total current number of disabilities caused by some of the major diseases under study in the National Institute of Arthritis and Metabolic Diseases and the estimated annual cost to the Nation

I. Deaths during 1961 (National Office of Vital Statistics) :

Category :

Diabetes mellitus.....	30, 098
Gastrointestinal diseases (ulcer of stomach and duodenum, and cirrhosis of the liver).....	35, 250
Total.....	65, 348

II. Disabilities (National Health Education Committee, Inc., 1962) :

Rheumatic diseases (259,000 persons completely disabled and 1,705,770 persons partially disabled)----- 1,964,700

III. Estimated annual economic cost to the Nation (National Health Education Committee, Inc., 1962) :

Rheumatic diseases (arthritis, rheumatism, gout)----- \$2,000,000,000

HIGHLIGHTS OF PROGRESS IN RESEARCH ON ARTHRITIS AND METABOLIC DISEASES—1962

Items of Interest on Research Studies Conducted and Supported by the National Institute of Arthritis and Metabolic Diseases

Most of the diseases within the province of the National Institute of Arthritis and Metabolic Diseases (NIAMD) are of chronic nature, and so pose a mosaic of problems. These diseases—arthritis, diabetes, and disorders of blood, bone, and liver, and the gastrointestinal tract, among others—require for their solution, comprehension of some of the intricate, fundamental mechanisms of the mainspring of life itself. Many of the complexities of the mechanisms, however, have yielded under meticulous day-by-day study by basic researchers and clinical investigators, though much more remains unanswered.

The following highlights of research—presented in nontechnical language and categorized under various disease headings for the convenience of the reader—represent an abbreviated forum in which are described the research efforts of a number of Institute scientists and grantees which are gradually fitting in the pieces of the complex puzzle of biology and medicine.

RHEUMATIC DISEASES

The various rheumatic diseases are the most common cause of chronic illness in the Nation, affecting about 11 million people. There has been an intensification of interest by scientists in the rheumatic diseases area, especially in the application of new and sophisticated research techniques to fundamental problems.

Institute scientists, for example, have reported encouraging results from the administration of the drug, methotrexate, to patients suffering from psoriatic arthritis. In the meantime, new knowledge of osteoarthritis has been gained from studies by Institute-supported scientists who have produced bone spurs by injecting cartilage debris in experimental animals.

Man's knowledge of one form of arthritis, gout, has been enhanced by Institute studies which have helped determine what causes the pain in acute gout and how the ancient drug, colchicine, works in relieving the inflammatory response.

ENCOURAGING RESULTS REPORTED IN METHOTREXATE THERAPY OF PSORIATIC ARTHRITIS

A preliminary report of a 4-year clinical investigation of the value of intermittently administered methotrexate (amethopterin) in psoriatic arthritis shows mild to marked improvement in most patients. Use of the drug was accompanied by generally mild but reversible side effects. By cautious parenteral therapy with the antifolic agent, NIAMD and National Cancer Institute scientists obtained these encouraging results in 15 of 18 patients with either psoriatic arthritis or coexistent psoriasis and rheumatoid arthritis. Seventeen of these patients had had previous corticosteroid therapy with unsatisfactory control.

Drs. William O'Brien, Roger L. Black, and Joseph J. Bunim of NIAMD's Arthritis and Rheumatism Branch, and Eugene J. Van Scott, and Arthur Z. Eisen, of NCI, reported the results of the study of 23 patients divided into 3 groups at the annual scientific session of the American Rheumatism Association. The efficacy of the drug in treatment of the psoriatic arthritic group and the coexistent psoriasis and rheumatoid arthritis group, contrasted sharply with the lack of improvement in patients with rheumatoid arthritis alone.

Although the well-known long-term toxic effects of prolonged oral antifolic therapy on bone marrow, intestinal tract, and possibly liver dictates cautious

use of methotrexate, the scientists believe the results of this study indicate that their dosage schedule and route of administration are effective enough to warrant further investigation under strictly controlled conditions.

BONE SPURS PRODUCED IN JOINTS OF DOGS BY CARTILAGE DEGENERATION PRODUCTS

NIAMD grantees have produced spurs and small bone cysts by injecting cartilage debris into the knees of experimental animals. Their preliminary study suggests that chronic chemical inflammation by cartilage degradation products may play an important role in the formation of spurs and other peripheral changes in degenerative arthritis.

The cause of marginal spurs in degenerative arthritis has long been obscure. It is well known that cartilage debris is worn away from the articular surface and can be found in the joint fluid and lining of patients with this condition. Previous investigation has shown that a single injection of finely divided cartilage into an animal's knee will produce a synovitis. Repeated injections of blood and various chemicals produce different reactions but, to date, none of these procedures had produced spurs unless the cartilage of the articular surface was damaged.

Dogs injected with cartilage suspension for less than 6 months developed only synovitis while injections continuing for 9 to 12 months produced the spurs and bone cysts.

These findings, by Drs. O. Donald Chrisman and Wayne O. Southwick of the Yale University School of Medicine, although preliminary, shed new light and warrant further investigation on the pathogenesis of spurs in osteoarthritis. Their work was presented at the annual meeting of the American Rheumatism Association.

BONE NECROSIS AS COMPLICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

Institute-supported scientists have reported that 11 patients in a series of 400 cases of systemic lupus erythematosus (SLE) developed aseptic bone necrosis. In all but one patient, the disease process, once begun, progressed insidiously and, in eight of the patients, led to severe joint damage.

Persistent localization of pain on motion to one hip or knee joint suggested the presence of bone necrosis rather than other usual complications of the underlying SLE. X-ray changes could be observed usually soon after the onset of symptoms. Increased density of the involved bone due to the death of tissue with secondary osteoporosis (bone thinning) was observed as an early manifestation of the disease. As the disease progressed, a subchondral necrosis was observed which progressed to eventual loss of the entire head of the femur or advanced degeneration of the femoral condyles. Although rest and salicylate therapy yielded symptomatic relief, there was no radiographic evidence of improvement, the grantees reported. Careful examination failed to establish a relationship between corticosteroid therapy and the beginning of bone symptoms.

The NIAMD-supported study, by Drs. Edmund L. Dubois and Lewis Cozen, of the University of Southern California and the College of Medical Evangelists, Los Angeles, was reported in the *Journal of the American Medical Association*.

ENIGMA OF HOW COLCHICINE STOPS GOUT ATTACKS EXPLAINED

NIAMD scientists have dramatically shown how the age-old drug, colchicine, may interrupt gouty attacks. Their studies reveal that colchicine acts on white blood cells, diminishing their phagocytosis of urate crystals in the affected area and thus reducing the inflammatory response that is characteristic of acute attacks.

Colchicine has been used for centuries to relieve acute gout, but its mechanism of action has remained an enigma. Also poorly understood is the relationship between the two main features of gout, the painful recurring attacks, and the inherited metabolic defect resulting in the accumulation of uric acid in the body. It has been known, however, that colchicine has no effect on uric acid metabolism.

The current work on colchicine's action, reported at the American Society for Clinical Investigation by Drs. Seegmiller, Howell, and Malawista of NIAMD's Arthritis and Rheumatism Branch, follows a series of findings by them beginning over a year ago when they reported that the injection of microcrystals of sodium urate would produce an inflammatory response in both gouty and nongouty individuals; in some cases, the result was indistinguishable from a spontaneous

attack. A constant feature of both the spontaneous and induced reaction was phagocytosis of the urate crystals and the production of large quantities of lactic acid when the leukocyte effusion from the involved joint was incubated *in vitro*.

The investigators have now found that the amount in this phagocytosis and inflammatory reaction is substantially reduced in volunteer patients who are treated with colchicine prior to injection of the crystals. Colchicine's anti-phagocytic action has been confirmed by a variety of *in vitro* techniques which include counting directly the number of crystals ingested by the white cells and also measuring the amount of carbon dioxide produced by the leukocytes after ingestion of labeled urate. Metabolic activity of the leukocytes was also determined by measuring the amount of labeled CO_2 they produced when placed in a medium of radioactive glucose. Normally CO_2 production would increase while the cells were phagocytizing, but no increase occurred when plasma from the same subject after he had received a therapeutic dose of colchicine was added to the medium.

The NIAMD investigators propose that "the diminished metabolic activity of the leukocyte in response to colchicine results in a diminished phagocytosis and lactic acid production, which serves to interrupt the cycle of new crystal deposition, inflammatory response, phagocytosis of crystals and increased acid production that seems to be essential for continuation of the acute attack of gouty arthritis."

HUMAN WHITE BLOOD CELLS FOUND CAPABLE OF BREAKING DOWN URIC ACID

Scientists at NIAMD have found that intact human white blood cells are capable of degrading uric acid in the human body. This finding may lead to a better understanding of uric acid metabolism in gout.

Despite the absence of the uric acid-degrading enzyme, uricase, in man, there is evidence that one-fourth to one-third of the uric acid produced in the body is metabolized to allantoin, ammonia, CO_2 and other products. Test tube studies of blood cell fragments by previous investigators have suggested that leukocytes may have the enzymatic equipment necessary for degradation or uricolysis, but there has been no conclusive demonstration that intact human leukocytes take part in uricolysis.

Suspensions of radioactively labeled sodium urate crystals were prepared, intact human leukocytes were added and then determinations of the extent of uricolysis were made. The leukocytes were found capable of liberating significant amounts of labeled carbon dioxide from the uric acid, indicating that uricolysis was taking place. Similar preparations of erythrocytes, or red blood cells, failed to show the same significant degradation.

The authors, Drs. J. E. Seegmiller and R. Rodney Howell of NIAMD's Arthritis and Rheumatism Branch, conclude that these studies provide strong evidence that leukocytes are capable of uricolysis in the body, probably through the action of veridoperoxidase, an enzyme present in the leukocytes. This finding may clarify the manner in which the human body metabolizes uric acid and lead to an understanding of the inherited defect in body chemistry which causes an accumulation of uric acid and the development of gouty arthritis. Their work is reported in the 1962 "Abstracts of the Federation of American Societies for Experimental Biology."

DIABETES

Diabetes is perhaps the best known and most important of the metabolic diseases. Few realize, however, that diabetes can be a significant killer and can often be accompanied by such complications as premature arteriosclerosis, kidney and liver disease, and damage to the blood vessels of the retina.

The bright side of diabetes is the knowledge researchers and clinicians are gaining of this disease. In the past year, for example, the concept of "prediabetes" has come into the forefront of scientific scrutiny.

This developing concept of prediabetes has been expressed in the statement: "Before you are born, you are prenatal; before you are diabetic, you are prediabetic." At present, Institute-supported scientists are perfecting methods to detect the prediabetic state in hopes of slowing the development of some of the grave complications of diabetes, or of delaying the onset of overt clinical diabetes.

METHODS FOR EARLY DETECTION OF PREDIABETICS DEVELOPED

NIAMD grantees have devised a group of test procedures to find the prediabetic individual before the glucose tolerance test becomes abnormal. Photography of conjunctival blood vessels and electron microscopy of ear lobe biopsies reveal characteristic pathologic changes which provide new diagnostic tools which could enable early treatment of prediabetic patients in hopes of preventing or delaying clinical diabetes.

The glucose tolerance test is a measure of carbohydrate metabolism and is used to detect completely asymptomatic diabetes patients. From a genetic standpoint, however, a person is probably prediabetic at birth, though he continues to have a normal glucose tolerance test for years. This developing concept of "prediabetes" has been expressed in the statement: "Before you are born, you are prenatal: before you are diabetic, you are prediabetic." Since it is conceivable that other body changes may antedate an abnormal blood glucose, the scientists studied other possible techniques for determining the prediabetic state.

Eighty-four subjects, with a mean age of 23 years, were studied with various screening procedures during a 2-year period. The group included 15 healthy nondiabetic persons, 15 diabetics, and 54 "prediabetics" chosen on a genetic basis according to consanguinity. In a significant number of these 54, both parents had diabetes and on the basis of other studies all of these would be expected to develop diabetes.

Ninety-two percent of the 54 patients showed a high venular-arteriolar ratio in ocular conjunctivae. (The bulbar surface of eyeballs normally has a 2-to-1 ratio of veins twice as large as arteries; in diabetic patients the ratio is 4 to 1.) Sixty-nine percent showed an elevated 2-hour blood sugar in the oral glucose tolerance test. Nine other possible indices tested showed much less correlation.

Electron microscopy of ear lobe biopsy specimens from prediabetic subjects also suggest that dilation and leakage of minute venules, changes not present in normal controls, are the first morphologic evidence of derangement of the vascular system. These findings by the investigators, Drs. R. A. Camerini-Davalos, Alexander Marble and associates at the Joslin Clinic in Boston, were reported at the annual meeting of the American Diabetes Association. The grantees suggest that if the prediabetic state can be detected prior to any observable disturbance in glucose metabolism, it may be a better time for institution of treatment in hope of preventing progression of overt diabetes and subsequent complications.

HIGH INCIDENCE OF DIABETIC DIATHESIS IN PREGNANCY REPORTED

Screening of 20,000 pregnant women by an NIAMD grantee has revealed an unexpectedly high incidence of abnormal glucose tolerance. The study suggests that pregnancy provides a unique opportunity for the study of latent diabetes mellitus.

In the past, claims have been made for the predictive value of minor deviations in glucose tolerance whether produced artificially by glucogenic steroids or naturally by diabetogenic conditions such as pregnancy. The latter effect has now been quantified in a contemporary investigation.

A long-term study designed to determine the incidence of asymptomatic diabetes in pregnancy by a NIAMD grantee has revealed an expectedly high incidence of abnormal glucose tolerance. Screening of 20,070 women registering for prenatal care at Boston City Hospital and at Boston Lying-in Hospital disclosed 146 such cases, or a corrected prevalence of 1 in 116 registrations. This is from four to eight times the observed rate of overt diabetes in pregnancy.

"Gestational diabetes" was determined on the basis of 3-hour glucose tolerance tests. Continuing observation of patients with this condition revealed that 28.5 percent developed frank diabetes mellitus within $5\frac{1}{2}$ years of delivery. This is a minimal figure since it does not take into account patients who dropped out of the study and the cumulative percentage which could be obtained if the subjects were followed for additional years.

The NIAMD-supported investigator, Dr. John B. O'Sullivan, of Boston City Hospital and Boston University School of Medicine, directed attention to the fact that this condition could appear temporarily in pregnancy as long as $5\frac{1}{2}$ years before development of the full blown diabetic disease picture. At the same time he emphasized that a continual followup may extend this latent period even further. The study was reported in the *New England Journal of Medicine*.

ELECTRON MICROSCOPE REVEALS INSULIN RELEASE MECHANISM OF BETA CELLS

NIAMD grantees, studying the effects of the antidiabetic drug tolbutamide on the structure of pancreatic beta cells in the rat, through the use of an electron microscope, have shown more clearly than ever before how the cells release insulin. The studies indicate no difference in the insulin release mechanism between stimulation by tolbutamide and by an elevated blood sugar, and support previous findings of others that tolbutamide accelerates insulin release.

Although oral sulfonylurea drugs such as tolbutamide are widely used in the clinical treatment of diabetes, their mode of action in lowering blood sugar is not fully understood. In diabetes patients, sulfonylureas apparently release enough insulin from the beta cells to maintain normal blood sugar; the high sugar present in their diabetic state, however, fails to stimulate release of adequate amounts of insulin. In order to understand better the role of beta cells, the NIAMD grantees studied what ultramicroscopic structural changes may occur in beta cells after tolbutamide and glucose administration.

Rats injected with tolbutamide were sacrificed in groups at various timed intervals, and portions of their pancreases were rapidly removed and prepared for microscopy. Measurements of the pancreatic insulin content and the insulin-like activity of the serum were also made simultaneously in order to correlate the functional status of the beta cells with their structural appearance.

The NIAMD grantees found that tolbutamide stimulation caused beta granules to be released from deep within the cell by an ejection process. The beta granules, surrounded by a membranous sac, appeared to migrate to the surface of the cell. The sac fused with the basement membrane of the cell, then ruptured, and released its granular contents into the extracellular space adjacent to a capillary. There the granules dissolved, apparently releasing insulin to the bloodstream since simultaneous biochemical assays demonstrated an increase in serum insulinlike activity.

The grantees, Drs. J. R. Williamson, P. E. Lacy, and J. W. Grisham of the Washington University School of Medicine, St. Louis, Mo., also observed that an amorphous material was clumped near the beta cells before the formation of the granules in sacs and they believe the material may be a precursor of insulin. The work appears in "Diabetes," and in "American Journal of Medicine."

OBESE PATIENTS MAY REQUIRE SECRETION OF MORE INSULIN THAN NORMAL TO MAINTAIN NORMAL BLOOD GLUCOSE LEVELS

Nondiabetic obese subjects have been found by NIAMD grantees to have and to sustain significantly higher levels of circulating insulin in response to glucose administration than nondiabetic normal subjects. The finding suggests that obese patients required increased amounts of insulin to maintain normal glucose levels, and may also provide a new tool to facilitate early detection of the pre-diabetic state.

Although many factors are undoubtedly involved in the causation of diabetes mellitus, a significant but still undefined relationship exists between obesity and the onset of diabetes in adults. Recent techniques, including an immunochemical assay perfected by the present NIAMD grantees, have made it possible to measure insulin in the blood reliably. In view of this, the grantees investigated possible differences in insulin response to glucose administration between nondiabetic obese subjects (with no family history of diabetes) and normal controls.

The investigators found that, although blood glucose levels behaved similarly in both groups, a distinct difference between the two groups was observed in the changes in serum insulin. Insulin levels in normal subjects rose slightly 15 minutes after glucose administration, but soon returned to normal levels within an hour and a half to 2 hours. In contrast, the insulin levels were initially higher in the obese subjects and after glucose infusion showed a marked and sustained rise; they were still highly elevated after 90-120 minutes. Throughout the experiment, blood glucose levels were similar and within normal limits for both groups.

Drs. J. H. Karam, G. M. Grodsky, and P. H. Forsham of the University of California School of Medicine reported these findings at the annual meeting of the American Diabetes Association.

OTHER METABOLIC DISORDERS

HISTIDINEMIA: A NEW METABOLIC DISEASE

NIAMD scientists have determined the metabolic block in histidinemia, an inborn error of metabolism first detected less than a year ago by diagnostic tests for phenylketonuria (PKU). The newly discovered disorder, possibly associated with a speech defect, may provide a tool for testing theories on the mode of development of the mental retardation of PKU.

The disease was first reported by H. Ghadimi et al., at Research Institute Hospital for Sick Children, Toronto, Ontario, in August 1961, when an assumed case of phenylketonuria brought to light two female siblings who had consistently elevated blood levels of histidine and excreted large amounts of histidine in their urine. Both children gave positive reactions to ferric chloride tests but had normal fasting blood levels of phenylalanine and showed no mental retardation.

Subsequent studies were done by Dr. Victor H. Auerbach and associates, NIAMD-grantees at Temple University Medical School and St. Christopher's Hospital for Children, Philadelphia, who reported the third case. Their work led them to suggest that the metabolic defect in histidinemia was the lack of histidase, the enzyme which converts histidine to urocanic acid. The NIAMD studies have now shown this to be true. Lack of this enzyme results in an inability to form formiminoglutamic acid (FIGLU), one of the sources for one carbon units utilized in the synthesis of purines and pyrimidines. The grantees also identified a number of histidine metabolites in the urine in histidinemia, one of which, imidazolepyruvic acid, is responsible for the false positive finding in the ferric chloride test for phenylketonuria.

Most recently NIAMD scientists have identified the enzymatic block in this newly discovered inborn error of metabolism. The investigators employed a little-used skin biopsy method to determine the missing enzyme in the disorder which is very similar biochemically to PKU and gives a false positive test for that disease.

The fourth and fifth cases were reported by NIAMD Arthritis and Rheumatism Branch investigators, Drs. Bert N. La Du, R. Rodney Howell, George A. Jacoby, J. E. Seegmiller and Vincent G. Zannoni.

Four of the five cases reported thus far have been female. Though all have been free of mental retardation, four of the five have speech defects. In the La Du series, which included the only male, the speech defect was associated with a shortened auditory memory and led the NIAMD investigators to suggest that perhaps this may be an instance where a metabolic disease is associated with a speech defect.

Biochemically, the condition resembles phenylketonuria. In both conditions an enzymatic block in the major metabolic pathway of an amino acid (histidine or phenylalanine) results in an increase in the formation of the corresponding keto acid by intermolecular transfer of amino groups. Both keto acids are excreted into the urine where they can be detected by the formation of a color complex on addition of ferric chloride.

Since none of the histidinemic patients is over 8 years old, it is presently impossible to predict the natural course or clinical spectrum of the disease on further development. Therefore, a collaborative project has been started by the NIAMD scientists with Dr. Carl J. Witkop, Jr., and Dr. Kenneth S. Brown, Section on Genetics, National Institute of Dental Research, to screen speech clinics at the University of Maryland and in the Montgomery County, Md., school system in search of additional undetected histidinemics. Because of the biochemical similarity of PKU and histidinemia, the newly detected disorder offers interesting possibilities as a testing ground for theories on PKU. For example, it may now be possible to test the theory that in PKU, the phenylalanine itself interferes with transport of amino acids to the brain and thus leads to mental retardation.

Dr. La Du, et al., reported their work in *Biochemical and Biophysical Research Communications*. The NIAMD grantees, Dr. Victor H. Auerbach, Dr. Angelo M. DiGeorge, Dr. Robert C. Baldrige, Dr. Charles D. Tourtellotte, and Dr. M. Prince Brigham, who also received support from the National Institute of Mental Health and the National Cancer Institute, reported their work in the *Journal of Pediatrics*.

IMPORTANCE OF GALACTOSE-FREE DIET FOR PREGNANT MOTHER WITH KNOWN
GALACTOSEMIC CHILD

NIAMD and National Institute of Neurological Diseases and Blindness scientists have studied the formation of cataracts—one of the signs of human congenital galactosemia—in offspring of rats fed a high-galactose diet. Their finding of a high degree of cataract formation supports previous suggestions of placental transfer of galactose, and also suggests the importance of a galactose-free diet for the pregnant woman carrying a probable galactosemic fetus.

Galactosemia is an hereditary disorder in which afflicted infants are unable to tolerate or metabolize galactose, a sugar present in milk, due to their lack of the enzyme galactose-1-phosphate uridyl transferase. If galactose is allowed to remain in the diet, it quickly creates a toxic condition leading to cataract formation, liver damage, irreparable mental retardation, and early death.

Previous researchers have conjectured that the galactosemic syndrome may begin in the uterus due to the passage of galactose through the placenta. This theory and experiments by other scientists showing that young rats on high-galactose diets develop cataracts—thus to some extent mimicking the galactosemic syndrome—led the NIAMD-NINDB investigators to study the extent of in utero damage to the rat fetus arising from a high-galactose diet by the mother.

Rats were fed a 40-percent galactose diet at various times in pregnancy and were continued on it until term (21 days). Galactose levels in blood were measured at term in the mothers and in the newborn which were delivered by cesarean section to avoid complications.

The scientists observed that all litters showed formation of cataracts at various stages, even in those offspring with as little as 3 days of maternal galactose feeding before term. No explanation was apparent for the finding that only minimal changes occurred in the lens of offspring whose mothers were on the diet since mating, whereas cataracts were very severe if the diet was started later in pregnancy. Other data also revealed that both fetal and maternal blood galactose levels were elevated and that fetal levels were very similar to that of the mothers.

This study, reported by Dr. Stanton Segal, of NIAMD's Clinical Endocrinology Branch, and Dr. Howard Bernstein, of NINDB, at a meeting of the American Society for Clinical Investigations, provides experimental evidence that galactose present in maternal blood has rapid and extensive access to the fetal circulation in the rat. These findings, if they can be extrapolated to man, also indicate that there may be in utero damage to the galactosemic fetus whose mother ingests galactose, thus suggesting the importance of a galactose-free diet for the pregnant mother of a known galactosemic child, since the developing fetus may also have the inherited inability to metabolize galactose.

INITIAL CHEMICAL REACTIONS IN PIGMENT FORMATION IN ALCAPTONURIA

Dr. Vincent G. Zannoni, Dr. S. E. Malawista, Dr. Bert N. La Du, and associates of the Arthritis and Rheumatism Branch, NIAMD, have worked out what is probably the first step in the biochemical mechanism responsible for production of the brown-black (ochronotic) pigmentation of the connective tissues in alcaptonuria. In addition they have postulated a scheme to explain the full sequence of events leading to ochronosis in alcaptonuric individuals.

Alcaptonuria is an inherited metabolic disease caused by the lack of a specific enzyme, homogentisic acid oxidase, necessary to convert homogentisic acid to maleylacetoacetic acid. This enzyme is missing at birth, but it is not until many years later that ochronosis, the brown-black pigmentation of the cartilage, tendons, and other connective tissues appears. It takes even longer before the patient develops degenerative arthritis of the spine and the large peripheral joints, characteristic for this disorder. Although these arthritic changes appear in the pigmented areas, no chemical relationship between the apparently inter-related conditions has as yet been established.

The NIAMD scientists developed a specific enzymatic method for measuring homogentisic acid (HGA) and used this technique to study the distribution of HGA and its metabolic derivative benzoquinoneacetic acid (BQA) in vivo and in vitro. Both HGA and BQA, when given intraperitoneally to guinea pigs, were distributed mainly into skin and cartilage. In vitro experiments, however, showed that BQA reacts chemically with skin and cartilage resulting in a change in its molecular structure to form products similar to those formed during the development of ochronotic pigmentation of the connective tissues in alcaptonuria.

In contrast to BQA, however, HGA is loosely bound to skin and cartilage and no chemical change takes place.

Further studies are now underway with purified collagen (connective tissue) preparations to determine the binding site of BQA within the tissues.

The study was reported in Arthritis and Rheumatism.

METHOD TO DETECT HETEROZYGOUS CARRIER OF WILSON'S DISEASE DEVISED

NIAMD grantees have developed a fairly reliable, quantitative method of identifying the heterozygous carrier of Wilson's disease. The system depends on the degree of incorporation of radioactively labeled copper into the plasma copper protein, ceruloplasmin.

Wilson's disease, a grave disorder transmitted by heterozygous parents who never developed the disease, is manifested, among other signs, by abnormal copper metabolism and a deficiency or absence of normal ceruloplasmins. Cirrhosis of the liver is always present in these patients and progressive damage to the nervous system occurs in many of them. These changes are associated with increased copper deposits in all body organs. The relationship between ceruloplasmins and other manifestations of the disease is not understood, but a much lower than normal incorporation of labeled copper into ceruloplasmin is found in patients with Wilson's disease.

The grantees devised a test procedure involving the administration of labeled copper as cupric acetate to 7 patients with Wilson's disease, 19 parents of patients, and 19 control subjects with no family history of the disorder. By measuring the rate of radioactive copper incorporation into ceruloplasmin at various times after ingestion, the investigators developed a numerical "ratio" method for distinguishing between the three groups. They found a ratio of 1.372 for the control subjects, 0.510 for the parents (heterozygotes), indicating a diminished incorporation, and 0.171 for the patients (homozygotes), an almost complete absence of incorporation.

Since the differences between the normal individuals and the heterozygotes were statistically significant, the NIAMD-supported investigators report that their method may be useful in determining whether parents, one of whom is known to be relative of a patient with Wilson's disease, may be capable of producing offspring in whom the disorder can develop. This work which could be of distinct practical value in genetic counseling, was reported by Dr. I. Sternlieb, of the Albert Einstein College of Medicine, New York, and his associates, in the Journal of Clinical Investigations.

IRREVERSIBLE LESIONS OF WILSON'S DISEASE AVERTED OR DELAYED BY EARLY DIAGNOSIS, TREATMENT

NIAMD grantees at the Albert Einstein College of Medicine, Yeshiva University, have reported that an excessive amount of copper in the liver is a valid diagnostic signpost, preliminary to the full onset of Wilson's disease, a rare in-born error of metabolism caused by the body's inability to control the absorption or excretion of copper. Dr. Irmin Sternlieb and Dr. I. Herbert Scheinberg further reported increasing evidence that the irreversible lesions of the disease can be averted, delayed, or minimized by early treatment designed to decrease the absorption of dietary copper and to promote excretion of existing deposits.

The current study is an extension of long-term investigations by the grantees on Wilson's disease. They previously developed a diet and treatment for the disease and demonstrated a method of detecting the heterozygous carriers of the disorder. The treatment consists of a low-copper diet and the administration of dietary potassium sulfide to bind ingested copper and make it unabsorbable. Oral penicillamine is also administered to promote urinary excretion of copper already deposited. Their system for determining Wilson's disease carrier depends on the degree of incorporation of radioactively labeled copper into the plasma copper protein, ceruloplasmin.

The Yeshiva group reported to the American Gastroenterological Association meeting that seven asymptomatic patients treated by their regimen for periods up to 5 years have shown no signs or symptoms of Wilson's disease. The presence of Wilson's disease in these asymptomatic patients was determined by a dual test, serum ceruloplasmin deficiency and excessive hepatic copper found on liver biopsy. Followup biopsies of two of the patients showed no change in liver histology although a marked decrease in hepatic copper concentration was ob-

served. They noted, however, that even 5 years are "too short for definitive evaluation of this regimen in a disease whose clinical onset may normally be delayed as long as the fifth decade." The seven patients ranged in age from 3½ to 31 years.

The NIAMD-supported investigators suggested that in the presence of a deficiency of the plasma copper protein, ceruloplasmin, a liver biopsy should be performed and the tissue analyzed for copper deposits. Excessive copper deposits indicate that Wilson's disease can be expected to develop and that the patient should be started on anticopper regimen as soon as possible in an attempt to forestall the onset of the clinical manifestations of the disease. A normal level of copper deposits in a suspected Wilson's disease patient indicates that the patient will not develop the disease.

The NIAMD grantees concluded that serum ceruloplasmin deficiency combined with high hepatic copper provides a reliable diagnostic indication of the familial disorder. It is of the utmost importance to make the diagnosis early so that effective treatment may avert development of the characteristic irreversible manifestations of hepatic, neurologic, and corneal involvement.

INSTRUMENT THAT SIMULTANEOUSLY MEASURES SWEATING RATE AND CONDUCTIVITY DEVELOPED

NIAMD scientists have devised an instrument that simultaneously measures the rate of sweating and the conductivity of electrolytes, predominantly sodium chloride, in the secretion. Preliminary data obtained from using this instrument on a small group of patients with cystic fibrosis support the hypothesis that a precursor solution of higher than normal electrolyte concentration is secreted and leads to the final high concentration of sweat salt in these patients.

One of the prominent clinical manifestations of cystic fibrosis is the elevated concentration of chloride in sweat. Because of this defect, patients with the disease have impaired ability to conserve salt, especially in hot weather, and may go on to cardiovascular collapse and death. It has been suggested that the defect may be either due to a disorder information of a precursor solution in the coil of the sweat gland or to impaired salt reabsorption from sweat gland tubules.

In an attempt to decide between these alternatives, Dr. Lewis E. Gibson, a visiting scientist at NIAMD and now a pediatrician at Johns Hopkins Hospital, and Dr. Paul A. di Sant'Agnese, Chief of NIAMD's Pediatric Metabolism Branch, developed their measuring instrument, the first of its kind. This device utilizes the sweat-stimulating plant substance, pilocarpine, which is made to enter a localized area of skin under the influence of electric current (iontophoresis). Attached meters measure the rate of excretion and the conductivity, or electrolyte activity, of the sweat.

Preliminary data obtained were consistent with a hypothesis that a precursor solution more concentrated than normal is formed in these patients and that the subsequent rate of reabsorption of electrolytes from the sweat gland tubules is normal. It would follow that since the tubules could return salt to the body at only normal rates from the more concentrated precursor solution, an elevated concentration of salt in the sweat would result.

The work is reported in the 1961 Transactions of the Society for Pediatric Research.

HIGH FUCOSE CONCENTRATION FOUND IN SWEAT MUCOPROTEINS FROM CYSTIC FIBROSIS PATIENTS

NIAMD scientists have demonstrated mucoproteins in human sweat and have found that patients with cystic fibrosis have a higher than normal concentration of the sugar fucose in their sweat mucoproteins. Further study of the little-known mucoproteins, fractions containing carbohydrate and protein, may be of value to CF diagnosis and to studies on genetic problems of this disease.

Cystic fibrosis is an inherited disorder affecting the exocrine body glands which include the sweat, tear, and salivary glands, as well as those associated with the pancreas, small intestine, and lungs. Previous studies had shown that mucoproteins taken from small intestine fluid of CF patients contain an abnormally high amount of fucose. The present preliminary studies of mucoproteins from CF sweat were made in hopes of revealing the nature of a common denominator for the many apparently unrelated manifestations of the disease in various body organs.

Sweat from 10 normal controls and 8 cystic fibrosis patients was collected during heat stimulation and immediately frozen in dry ice to prevent the degradation of heat-sensitive material before precipitation. The resulting material showed the presence of a carbohydrate-protein complex containing galactose, N-acetylgalactosamine, and sialic acid in equal molecular amounts in both groups of patients. However, while there were only negligible traces of fucose in normal sweat, significant quantities of the sugar substance were present in CF sweat, thus suggesting some defect of mucoprotein metabolism in the disease.

The work by Dr. J. C. Pallavicini, Dr. O. Gabriel, and Dr. P. A. di Sant'Agnese of NIAMD's Pediatric Metabolism Branch appears in the 1962 Abstracts of the Federation of American Societies for Experimental Biology.

NEW ENZYME DEFICIENCY IN CYSTIC FIBROSIS REPORTED

NIAMD-supported investigators at Northwestern University Medical School and Chicago Medical School have discovered in children with cystic fibrosis (CF) a hitherto unknown deficiency of a fat-splitting enzyme, normally active in the circulation, lipoprotein lipase. They have shown that CF patients are unable to clear from the blood an intravenous load of fat as satisfactorily as normal control subjects, especially following the administration of heparin, an anticoagulant known to activate the fat-clearing function of the enzyme whenever it is present.

In a group of normal and CF children, the investigators observed a steady increase in total blood fats, primarily triglycerides, during loading with Lipomul (a commercial fat mixture containing cottonseed oil, dextrose, water, and emulsifiers). After fat loading was discontinued, blood fat levels returned to normal within 24 hours. Although some fibrocystic subjects showed clearing curves which were high and prolonged others were within the normal limits.

Because it had been demonstrated previously that heparin could trigger a fat clearing factor in the blood within a few seconds during one circulatory cycle, the NIAMD grantees compared the ability of different groups of subjects to clear a fat load after heparin administration. In a group of normal heparinized children, blood fat reached only half the concentration during loading as the non-heparinized group and returned to near-normal levels within 6 hours. In contrast with this, in a group of five heparinized CF children the blood fat levels of four patients were essentially unchanged by the heparin and clearing curves resembled the curves of the non-heparin-treated group.

Direct measurement of plasma lipoprotein lipase failed to show a satisfactory rise following heparin among fibrocystic patients as compared with normal controls.

Since it has been known that the failure of CF patients to absorb ingested fats from the intestine is due to a deficiency of pancreatic lipase, the grantees suggest that their findings may be explained on one of the two bases: Either the lipase deficiency in CF is more widespread than hitherto believed and involves other organs in addition to the pancreas, resulting in a generalized deficiency of more than one lipase; or poor intestinal absorption of triglycerides over a long period of time results in lack of stimulation and mobilization of lipoprotein lipase within the circulation.

The investigators, Dr. David Yi-Yung Hsia, Miss Joan Slack, Dr. Sumati Nair and associates reported their findings in the *Journal of Laboratory and Clinical Medicine*.

GASTROENTEROLOGY

Disorders of the gastrointestinal system, which may range from stomach upset to peptic ulcer and ulcerative colitis, are probably the most frequent of the ills that man is heir to, except perhaps for the common cold. These disorders are not major killers and cripples such as cancer, heart disease, and arthritis, but their cumulative morbidity is serious enough to warrant full investigation and complete understanding.

Until recently, however, research in the physiology of digestion and treatment of gastrointestinal disorders has not been the prime concern of biomedical scientists. Gastroenterology research today is in a state of dynamic transition from the mild interest of a few years ago to today's renewed excitement, and a significant portion of this renaissance has been stimulated by the active support extended to this field of endeavor by the National Institute of Arthritis and Metabolic Diseases.

Progress ranges from such therapeutic advances as the reported healing of duodenal ulcers by a new technique involving freezing of the stomach mucosa, to the development and use of new diagnostic tools in the direct examination of the gastrointestinal tract.

DUODENAL ULCERS HEALED BY FREEZING STOMACH MUCOSA

In preliminary studies of an unusual therapeutic technique, NIAMD grantees have been able to produce healing of duodenal ulcers in 35 patients during the past year by a simple and effective technique of freezing stomach mucosa for short periods of time. The technique, which involves the perfusion of frigid liquid through tubing attached to a balloon in the patient's stomach, has resulted in "physiological gastrectomy" without loss of the stomach, since symptoms and signs of duodenal ulcers disappeared after treatment.

Previous clinical work by NIAMD grantee Dr. O. H. Wangensteen and his colleagues at the University of Minnesota Medical School, Minneapolis, had shown that massive gastric hemorrhage can be controlled by gastric cooling, a process also observed capable of suspending gastric digestion. These findings prompted the grantees to study whether a duodenal ulcer might heal if the balloon treatment could be used with a coolant at lower temperatures.

A technique was developed by which tubing and a balloon could be passed through a patient's anesthetized throat to the stomach. Experimental trials made first with more than 150 dogs showed that a coolant mixture of absolute alcohol and ice water, perfused through the inflow-outflow tubing to maintain a gastric mucosal temperature of -17° to -20° C. ($+1.4^{\circ}$ to -4.0° F.), was capable of suppressing gastric secretion. Various temperatures, time factors and safety limits of cooling were studied, and other determinations were made to develop an optimal method.

In preliminary clinical trials, the NIAMD-supported investigators found that after about 1 hour of freezing of the gastric mucosa, symptomatic relief occurred within 2 hours, followed later by X-ray evidence of healing of duodenal ulcer craters. Effective depression of gastric secretory responses has occurred regularly. Although absence of hydrochloric acid from the gastric secretions (achlorhydria) has not been found uniformly, nearly all patients have shown at least a 50-percent decrease in free hydrochloric acid in overnight secretion. Patients treated in this manner for their ulcer are allowed a general diet but are cautioned to be sparing in the use of alcoholic and caffeine-containing beverages.

The grantees, whose work appears in the *Journal of the American Medical Association*, volume 180, No. 6, and in the proceedings of the recent meeting of the American Surgical Association, report that it is too early to determine whether permanent healing results. Since no harm from the technique has been observed in either dog or man and it can be repeated if ulcers recur, it is possible that this new procedure will generally avoid the need for surgery by gastrectomy in uncomplicated duodenal ulcers.

FIBERSCOPE PROVIDES NEW DIAGNOSTIC TOOL FOR ULCERS, OTHER STOMACH DISORDERS

NIAMD grantee Dr. Basil I. Hirschowitz of the University of Alabama Medical School, Birmingham, Ala., has devised a new endoscope, the "fiberscope," which superficially resembles the gastroscope. It is equipped with a head, comprising a lamp bulb, a prism, and a compound lens which focuses the image. Its shaft contains a fiber optic system which transmits images through a bundle of parallel optical glass fibers to the eyepiece. The fiberscope has high light transmission and good contrast even when the instrument is acutely curved, allowing still and motion pictures to be taken in color.

The instrument is completely flexible throughout its entire length and permits easy passage and patient comfort. The entire stomach, as well as areas not previously observed by endoscopy—the pyloric canal, duodenal bulb, and the jejunal loops created by gastrojejunostomy—are accessible.

Dr. Hirschowitz's observations, as reported at the recent World Congress of Gastroenterology at Munich, include the finding of a sphincter or ringlike muscle at the apex of the duodenal bulb which may be related to the localization of ulcers in this area. The NIAMD grantee also recognized and classified three types of duodenal ulcers: acute, chronic, and the indolent or apparently "incurable" form. An interesting finding was the high incidence of postgastrectomy

pathology, the majority undiagnosed radiologically and often clinically unsuspected.

An account of this NIAMD-supported work, has appeared in the *Lancet* and other journals. The grantee is presently developing a similar instrument for pediatric use and a flexible fiber esophagoscope based on the same principle.

SILICONE MOLD METHOD PROVIDES UNIQUE DIAGNOSTIC TOOL FOR LOWER BOWEL DISEASES

Grantees supported in part by NIAMD have developed a remarkably reliable method for detecting or clarifying the character of sigmoid colon and rectal lesions which are either indefinitely recognized or totally undiscerned by diagnostic X-ray examination. The technique consists of a silicone foam enema which jells in the colon to form a mold, taking on the contours of the bowel and giving an accurate, detailed imprint of the mucosal lining.

The enema contains a radiopaque mixture of two forms of silicone rubber, a diluent that softens the mold, and an oxidizing agent which polymerizes the silicone and jells the mixture. Since the mold has a soft foamy consistency, it is evacuated spontaneously, usually within 15 minutes of administration, even through constricting lesions. Irregularities of the colon are clearly revealed on the mold surface, and any cells sticking to it can be washed off and examined microscopically.

More than 80 persons, ranging in age from 6 to 81 years, have been examined with the technique and have shown various chronic abnormalities, including polyps, adenocarcinoma, ulcerative colitis, and diverticula.

Since the NIAMD grantees at this stage of their experience have been primarily concerned with evaluating its efficacy and safety, many of their patients had colonic lesions which could be, and were, diagnosed by existing methods.

The NIAMD-supported investigators, Drs. Galen B. Cook and Alexander B. Margulis of Washington University School of Medicine, St. Louis, have reported that they are now attempting to eliminate air-pocket artifacts and to develop methods to use this practical adjunct to clinical diagnosis elsewhere in the gastrointestinal tract. Their work appears in the *American Journal of Roentgenology*.

PANTOTHENIC ACID INJECTIONS REDUCE INTESTINAL DYSFUNCTION AFTER EXPERIMENTAL SURGICAL STRESS

NIAMD grantees have found that injections of the B-complex vitamin, pantothenic acid, significantly reduces the duration of intestinal dysfunction (paralytic ileus) in dogs after abdominal surgery. Use of the vitamin following human surgery is being tested.

Paralytic ileus after abdominal surgery is manifested by a decrease in intestinal motility (peristalsis) which may lead to more serious complications. Surgical stress is believed to increase requirements of pantothenic acid, which, although it has no direct effect on peristalsis, is necessary for acetylcholine formation. Acetylcholine aids in the transmission of nerve impulses across synapses, thereby stimulating and maintaining peristalsis. Various experimental studies have indicated that the storage of pantothenic acid may be limited, so that subclinical deficiencies might become manifest during a period of increased requirement.

NIAMD grantees have significantly reduced the duration of postoperative adynamic ileus in dogs by administering D-pantothenyl alcohol, the injectible form of the B-complex vitamin, pantothenic acid. The grantees suggest that D-pantothenyl alcohol may prove useful in treating adynamic ileus in humans, and this suggestion is undergoing controlled clinical trial.

A few individual case reports have indicated the beneficial effects of D-pantothenyl alcohol in the treatment of ileus following surgical stress. In order to determine the effects of the B vitamin in a controlled laboratory study, the NIAMD-supported investigators devised a consistent method for producing paralytic ileus and determining the duration of the condition in dogs.

The NIAMD grantees, Dr. Michael A. Polacek and his associates at the Marquette University School of Medicine, Milwaukee, believe the study indicates that physical trauma to the intestine resulted in excessive utilization of available pantothenic acid stores, since prolonged ileus was largely prevented by administration of pantothenic acid. Since no clinical recommendations can be made on the basis of this study, extensive double-blind clinical trials of pantothenic acid

using a similar method are being made in patients undergoing biliary tract, gastric, and gynecologic surgery.

CIRCULATING ANTINUCLEAR GLOBULINS IN ULCERATIVE COLITIS DEMONSTRATED

NIAMD grantees studying sera from 24 patients with ulcerative colitis have found that 18 of them (75 percent) exhibited circulating antinuclear globulins, protein fractions which react with nuclei from white blood cells similar to the way in which antibodies react with their antigens. Although it is not known what role the globulins play in ulcerative colitis, their presence offers further evidence for an altered immunological state in this disease.

Many previous studies have supported the thesis that hypersensitivity factors are involved in the etiology of ulcerative colitis. The fact that many such patients sensitive to drugs and blood transfusions, are benefited by ACTH and corticosteroids, and often have concurrent disorders such as leukopenia, hemolytic anemia, and arthritis suggests the existence of an altered immune state. In the course of studying patients with various disease for antileukocyte factors, two individuals with ulcerative colitis were found by the NIAMD-supported investigators to have circulating antinuclear globulins. Their present study was done to determine further the nature and frequency of these abnormal globulins in ulcerative colitis patients.

Sera from the 24 patients were assayed for the presence of antinuclear globulins by two complex fluorescent antiglobulin methods, one which measured the affinity of the sera for human leukocyte whole nuclei, and another its affinity for calf nucleoprotein. Eighteen subjects showed the presence of antinuclear globulin on the leukocytes but no reaction was detected with the calf nucleoprotein procedure. Negative reactions were also seen in over 250 sera from healthy subjects as well as from patients with leukopenia, hyperglobulinemia, and many other disorders. Although many of the patients exhibited some of the features attributed to hypersensitivity disorders, the LE cell test for lupus erythematosus was negative and the rheumatoid factor was absent in all cases.

The grantees, Dr. Paul Calabresi and his associates at the Yale University School of Medicine, New Haven, Conn., reported this work in the *Journal of Clinical Investigation*.

CAUSE OF BLOOD PROTEIN LOSS IN WHIPPLE'S DISEASE SHOWN

NIAMD and National Cancer Institute scientists have clarified the nature of hypoalbuminemia, an abnormally low content of the protein albumin in blood, in association with Whipple's disease. The scientists have found that hypoalbuminemia is largely due to excessive protein loss in the gastrointestinal tract, and that this loss can be reversed rapidly by adrenocorticosteroid and antibiotic therapy.

Whipple's disease is a grave metabolic disorder with loss of weight and strength characterized by a defect in intestinal absorption of fat. Hypoalbuminemia is frequently associated with the disease. In order to explore further the nature of hypoalbuminemia, the NIAMD-NCI scientists studied five patients to determine whether protein was lost in the gastrointestinal tract.

Intestinal protein loss was determined by intravenously injecting albumin labeled with radioactive chromium. Since chromium, whether free or bound to protein, is not absorbable by the intestine, the amount of radiochromium which appears in the feces is an index of the amount of albumin which leaked into the gut. The investigators found that the patients with Whipple's disease lost between 1.3 and 22.1 percent of the injected labeled albumin in the stool, as compared with isotope (protein) loss of between 0.1 and 0.7 percent for 25 control subjects with normal serum albumin concentrations. This finding suggests that intestinal protein loss has an important role in the development of hypoalbuminemia. Impaired albumin synthesis may be a contributing factor, as revealed in other labeled albumin studies by the same workers, using radioiodine.

Previous investigations have shown that the administration of adrenocorticosteroids together with antibiotics brings about a remission of Whipple's disease. The present investigators, Dr. Leonard Laster, Dr. L. F. Feuster, and Dr. J. W. Singleton of NIAMD's Arthritis and Rheumatism Branch, and Dr. T. A. Waldmann of NCI, now have demonstrated that with the onset of this therapeutically induced remission, the intestinal loss of protein subsides and the patients' blood albumin returns to normal levels. Their work was reported before the recent annual meeting of the American Gastroenterological Association.

Also reporting before the meeting were NIAMD grantees, Dr. J. M. Ruffin and his associates from Duke University Medical Center, Durham, N.C., who have treated and followed 10 patients with Whipple's disease since 1954. Their studies indicate that antibiotics rather than adrenocorticosteroids seem to be the effective agent against Whipple's disease. The only deaths reported were two patients who received steroids only, while the other eight are alive and well following the administration of antibiotics and steroids or antibiotics alone.

B₆ VITAMIN ESSENTIAL TO INTESTINAL ABSORPTION OF TWO AMINO ACIDS

A preliminary study by an NIAMD grantee has shown that one of the B₆ vitamins, pyridoxal-5-phosphate, is essential to the active intestinal absorption of at least two amino acids in the intact animal. The study, by Dr. Francis A. Jacobs, of the University of North Dakota School of Medicine, suggests that one aspect of clinical B₆ deficiency might be inability to absorb amino acids from the intestine.

Vitamin B₆ is known to play a role in the active process of cellular uptake of amino acids. But it has not been apparent that amino acid absorption in the upper small intestine of the living animal is an active process dependent upon at least one of the B₆-vitamin factors.

In order to study intestinal absorption of amino acids in the intact rat, a perfusion technique was devised which permitted simultaneous study of both continuous absorption and absolute amount absorbed. The technique also allowed investigation of protective as well as alleviate effects of the B₆-vitamin factors against antimetabolite action.

In this study intestinal absorption of the two amino acids tested, L-methionine and L-tyrosine, was depressed by dietary pyridoxine deficiency, by the antivitamin deoxypyridoxine, and by the antimetabolite, 2,4-dinitrophenol (DNP). Simple pyridoxine deficiency or deoxypyridine-induced inhibition of absorption could be alleviated by treatment with pyridoxine. However, only pyridoxal phosphate would alleviate DNP-induced inhibition. On the basis of these observations Dr. Jacobs suggests that the B₆ vitamins play their role in the absorption process in the form of the pyridoxal phosphate. The study is reported in the *Journal of the American Medical Association*.

BILIARY AND PANCREATIC SECRETIONS VOLUMES MUCH HIGHER THAN PREVIOUSLY THOUGHT

NIAMD grantees have found that 24-hour bile output of apparently normal human livers varies between 1,000 and 2,000 milliliters per day, a quantity much higher than the value of 500 milliliters, usually stated in textbooks. By using a new technique to collect and measure biliary-pancreatic secretions, the investigators also found that daily normal pancreatic secretions amount to 1,500 to 3,000 milliliters and occasionally as much as 4,000 milliliters. These amounts likewise are far greater than the 100 milliliters quoted in the literature. The abundant electrolyte concentration of such large volumes of fluid explains the serious and occasionally lethal effect that follows loss of pancreatic juice either on establishment of fistulas or through prolonged vomiting.

Drs. Henry Doubilet and Louis Fishman, of the New York University School of Medicine, used a specially designed tube which permits complete collection of bile and pancreatic juice for measurement, then reinjects each sample into the duodenum, while maintaining the normal digestive process. In their studies, bile and pancreatic juices were collected at frequent intervals during a 24-hour period in ambulatory patients eating three meals a day.

The investigators believe that the low values previously reported for bile secretion were due to the collection technique in which bile was removed through a fistula and not returned to the duodenum. They point out that about 90 percent of the bile salts secreted into the intestine are reabsorbed and then circulated back to the liver for use in the formation of more bile. When bile is lost via the fistula method, circulation of bile salts is terminated and the liver must produce anew the bile salts secreted. Under these circumstances the daily secretion is reduced, and amounts to 400 to 600 milliliters. The new technique maintains the normal circulation of bile salts and relieves the liver of the need for producing additional salts.

The results of the biliary-pancreatic secretion studies were reported in the *American Journal of Gastroenterology* and the collection technique was described in the *Proceedings of the Society for Experimental Biology and Medicine*.

NATURE OF SYMPTOMATIC HEARTBURN CLARIFIED

NIAMD grantees, studying 12 patients with complaints of heartburn, have found that the symptom occurred when acidity was high in the esophagus and disappeared when the acidity decreased. This finding was obtained through the development of apparatus to measure simultaneously pressure within the stomach and esophagus, as well as esophageal acidity during the patient's complaints of heartburn.

Some of the hypotheses advanced to explain the development of heartburn include disordered motor function of the stomach or esophagus, oversecretion of hydrochloric acid, and a backflow of gastric contents into the esophagus. However, a number of difficulties have hindered the proper assessment of these factors. In order to clarify symptomatic heartburn, the NIAMD-supported investigators developed their apparatus to measure both pressure (which may produce distention or enlargement of the esophagus, previously thought to be the cause of heartburn) and pH (degree of acidity) within the esophagus.

Studies on 12 patients with histories of moderate to severe heartburn were performed by passing a pH electrode wired to a meter and other sensitive tubular devices through the nose to measure and record pressure and pH. Each subject was given a signal switch to depress whenever and for as long as he experienced heartburn.

The grantees, Drs. S. G. Tuttle, A. Bettarello, and M. I. Grossman of Wadsworth Hospital, Veterans Administration Center, and the University of California, Los Angeles, found that heartburn was associated with a fall in pH below 4 while symptoms disappeared when the pH rose above this level, thus indicating that gastroesophageal acid backflow results in heartburn. Their work appears in the Journal of the American Medical Association.

BASIC RESEARCH

Progress in research makes it increasingly evident that underlying all the biomedical fields is a substructure of fundamental knowledge common to the preclinical and clinical sciences. Obtaining this basic knowledge is one of the prime activities of this Institute.

Despite the gratifying progress being made in controlling some of the important diseases, there is still far too little known about their fundamental cause and nature. Much of this needed knowledge must come from basic research, from elucidation of the fundamental physical, biochemical, and physiological facts which make up the basic fabric of all the biological and medical sciences.

The variety of studies in this basic area is mirrored in such current Institute findings as the demonstration of antiplatelet antibodies, which has immediate clinical applicability, to further elucidation of the genetic code. The latter study at present is not directly related to the understanding of disease processes, but its implications will impinge strongly in the future on the entire field of heredity and inherited diseases.

UNIVERSAL GENETIC CODE MAY GOVERN CELL DEVELOPMENT

Dramatic evidence that the life-forming genetic code may constitute a common "language" understood by all living things has been reported by University of California and NIAMD scientists in a collaborative study. The study may have far-reaching implications, particularly in simplifying the task of researchers in many centers who are making rapid progress in deciphering the code itself.

The investigators, working with tobacco mosaic virus, extracted some of the ribonucleic acid (RNA) that directs virus replication by the plant cells and introduced the viral RNA into a "protein-incorporating system" extracted chemically from *Escherichia coli*, a common single-celled bacterium. Included in the *E. coli* system are amino acids, enzymes, larger enzyme-rich particles called ribosomes, transfer RNA (a special form of nucleic acid that helps translate the genetic code into actual protein synthesis), along with a few relatively simple chemicals needed to activate the complete reaction.

Normal deoxyribonucleic acid (DNA), the form of nucleic acid that normally carries the genetic "message" in bacteria and in the genes of all organisms, including man, was replaced in the system by abnormal RNA from the tobacco mosaic virus.

The result was a 75-fold stimulation in protein synthesis at the direction of the viral RNA. Radioactive labeling of the amino acids with carbon-14 indicated that the new protein was strikingly similar to tobacco mosaic virus protein.

The scientists, Drs. Akira Tsugita and Heinz Fraenkel-Conrat of the University of California, and Marshall W. Nirenberg and J. Heinrich Matthaei of NIAMD, report that this and other evidence for marked structural similarity between proteins synthesized by the *E. coli* system and by the tobacco plant under the direction of the same RNA "clearly indicates that the genetic code is quite similar for widely divergent organisms, and thus may be universal."

The present work, reported in the Proceedings of the National Academy of Sciences, was accomplished through preparation of the viral materials in Berkeley, air shipment of viral RNA to NIAMD for incorporation into the bacterial system, and air shipment again to Berkeley for analysis of the resulting products.

PLATELET ANTIGENS AND DISEASES CAUSED BY ANTI-PLATELET ANTIBODIES DEMONSTRATED

NIAMD scientists have clearly demonstrated for the first time that blood platelets contain many specific inherited antigens, at least seven of which are unrelated to red cell antigens which divide human blood into the well-known major blood types. They have also found that antibodies formed against platelet antigens can cause diseases and clinical complications which are in many respects similar to disorders caused by antibodies against red cell antigens.

It has long been known that individuals have antigenically different red blood cell types and that an individual exposed to a type different from his own may develop an antibody against it. These antibodies are easily demonstrated through the agglutination test (visual clumping of the cells). Other formed blood elements, such as platelets—which are involved in preventing leakage of blood from vessels—have been suspected of containing specific antigens, but up to now there has been no satisfactory technique available to demonstrate these antigens.

In order to study the problem of platelet antigens, Dr. N. R. Shulman and his associates in NIAMD's Clinical Hematology Branch developed a sensitive technique for detecting antiplatelet antibodies which depends on complement fixation rather than agglutination, the latter being unsatisfactory for platelet detection.

With the complement fixation test the NIAMD researchers have shown that most cases of platelet deficiency and bleeding in newborn infants (neonatal thrombocytopenic purpura) are due to an antiplatelet antibody formed in the mother against an antigen on the baby's platelets inherited from the father and foreign to the mother. In the families studied, the mother's antibody was transmitted through the placenta and caused bleeding in the infant by destroying the infant's platelets. Thus the etiology of this disease was shown to be quite similar to that of anemia in infants caused by mother-fetal incompatibility of the red cell Rh antigens.

The NIAMD scientists, reporting in the Journal of Clinical Investigation have also found that in blood transfusions, platelet antigens frequently are mismatched and may provoke antibodies which destroy platelets in subsequent transfusions—just as mismatched red cells are destroyed. Destruction of platelets by these antibodies can be the cause of some transfusion reactions and is frequently responsible for failure of patients with a platelet deficiency to respond to the newly developed technique of platelet transfusion.

STUDY EXPLAINS WHY SICKLE CELL HEMOGLOBIN CAUSES BLOOD CELLS TO BECOME DISFIGURED

Molecules of sickle cell hemoglobin have been found to change their "architecture," through a change in protein bonding, when warmed from 0° C. up to body temperature. This finding, by Dr. Makio Murayama of NIAMD, supplies the basic explanation for the way in which these abnormal molecules cause red blood cells to twist, and hints at a method of bringing some relief to patients during active stages of sickle cell disease.

Sickle cell disease is an inherited disorder in which red blood cells are distorted to an elongated shape when they are not carrying oxygen. Because of their crescent shape they frequently obstruct blood capillaries and bring on

the periodic hemolytic crises and anemia which occur in sickle cell patients. Early electrophoretic studies of the disease were done by Dr. Linus Pauling and coworkers, who first observed that the polypeptide portion of the hemoglobin in these patients was abnormal, suggested that this could lead to cellular distortion and coined the term "molecular disease." Their work opened up the whole field of study of abnormal hemoglobins, and since then many types have been identified.

Dr. Murayama's interest has been in the physical-chemical properties of sickle cell hemoglobin and stemmed from his early observations that deoxy-generated sickle cell hemoglobin gels at normal body temperature but liquifies when cooled to 0° C. This unusual behavior suggested that, as the molecules approach body temperature they undergo a change in three dimensional architecture, causing them to aggregate and produce the gel. His studies have now confirmed that such a structural change does take place. The studies were made possible by the technique of optical rotary dispersion, a process using the wavelength of light to measure the degree of rotation of plane polarized light.

The NIAMD investigator's finding more fully explains why the presence of sickle cell hemoglobin leads to twisted red cells and the resulting physiological consequences. The fact that the molecules of sickle cell hemoglobin are defective has been known for several years. Indeed, the precise biochemical defect—the interchange of a single amino acid, valine for glutamic acid, in the long-chained molecule—was uncovered by V. N. Ingram and others. What had not been established, however, was why this amino acid interchange produced the results it did, since similar interchanges have been seen in other abnormal hemoglobins and apparently cause no difficulty.

According to Dr. Murayama's work, the key to this question lies in the particular position at which the amino acid interchange takes place, the sixth position on the beta polypeptide chain. The sixth position happens to be the center of the bonding of the chain, and the interchange affects this bonding in such a way that as temperature changes, the bond changes, and thus the molecule assumes a different shape. Because of the particular shape of the molecules at body temperature due to the unusual bonding, they will aggregate within the red cell, stacking up and twisting the cell into its characteristic sickle shape.

The NIAMD study also provides a rationale for using localized cooling in sickle cell patients during crises, since their hemoglobin will unsickle at lower temperatures. Whether this type of therapy could bring some relief to these patients is unknown, however, since it has not yet been clinically tested.

A report of Dr. Murayama's work has been published in *Science*.

STABILIZATION OF BLOOD CLOTS FURTHER CLARIFIED

Studies by Drs. Koloman Laki and N. Chandrasekhar of NIAMD's Laboratory of Physical Biology have provided experimental evidence that the Laki-Lorand Factor (LLF), a normal constituent of blood, is essential to the formation of a stable blood clot. The studies also suggest that the carbohydrate residues from the clot precursor material, fibrinogen, play a role in the formation of the stable clot.

Thrombin is now believed to be involved in the clotting process twice: not only does it split off fibrin molecules from fibrinogen to form the primary clot, but recent studies have suggested that it may activate LLF into an enzyme which "vulcanizes" the clot by introducing strong bonds between the fibrin (or clot) molecules.

The NIAMD scientists have now found evidence for such a relationship in studies involving bovine fibrinogen treated with the enzyme sialidase which removes sialic acid, one of the carbohydrate components of fibrinogen. When this sialic acid-free fibrinogen was clotted with thrombin in the presence of LLF; it yielded a clot easily soluble in urea, a solution used to test clot solubility. This was in contrast with untreated fibrinogen which yielded a normal, insoluble clot, indicating that LLF may not be able to act on the sialic acid-free fibrinogen to produce a normal insoluble clot.

It was also shown in addition that higher concentrations of LLF in the clotting mixture resulted in an increased release of carbohydrates, thus further implicating LLF as an active agent in the release of carbohydrates during clotting. These studies, which the NIAMD scientists reported in *Biochimica and Biophysica Acta*, represent an additional clarification of the complex biochemical reactions involved in the formation of stable blood clots.

ROLE OF PEPTIDE B IN MICROCIRCULATION AND BLOOD CLOTTING

Studies by NIAMD scientists suggest that peptide B may play a vital role in the control of blood circulation in capillaries because of its action on smooth muscle contractions.

In order to clarify the mechanisms that control circulation of the blood through capillaries, NIAMD scientists studied the possible role of peptide B, known to be released during the conversion of fibrinogen to the clot-forming blood protein, fibrin. To test its action on smooth muscle such as is found in capillary walls, the scientists used rat uterus muscle in an experimental system capable of measuring muscle contraction. Peptide B of bovine origin acts as a strong potentiator of bradykinin, a naturally occurring peptide capable of inducing smooth muscle contraction.

Segmenting the peptide B molecule into two pieces did not impair its pharmacological activity. The scientists also succeeded in isolating a human counterpart of peptide B, and have found that it is three times more active than the bovine substance in the same test system. Tests are underway to locate the amino acid groups responsible for the activity of both the human and bovine molecules.

These studies by Drs. Jules A. Gladner, Albert J. Osbahr, Koloman Laki and associates of NIAMD's Laboratory of Physical Biology, have indicated that peptide B is a true physiologically active peptide, released by enzymatic cleavage from a normal blood constituent, fibrinogen, during its conversion to fibrin. The enzyme catalyzing this reaction is thrombin. The physiological advantage of capillary constriction to assist blood clotting is evident, but the scientists also postulate that since the fibrinogen-fibrin transformation is constantly going on in the body, to some extent, the reaction may have some relation to continuous control of the smooth muscle in capillary walls.

Their work was reported at the recent Ninth International Congress of Hematology, and appears in the *Annals of the New York Academy of Science*.

DIRECT EVIDENCE FOUND FOR LONG LIFESPAN OF LYMPHOCYTES

NIAMD scientists and the Department of Clinical Pathology, Clinical Center (CC) have found direct evidence for a long lifespan of both small and large lymphocytes in the rat. The study, based on a method of labeling lymphocytes, may be of great significance in understanding their protective role in the body.

Lymphocytes are formed in the lymph nodes and are present in large numbers in the blood and in smaller amounts in the wall of the intestine and other locations. They migrate to sites of chronic inflammation, but their function is unknown. The lifespan of lymphocytes is also nuclear and has been a subject of controversy for many years; previous estimates of lymphocyte survival have ranged from 170 minutes to 100 days.

Lymphocyte reutilization, i.e., the possibility that a lymphocyte utilizes components of old cells to form new ones, has hindered previous studies. The NIAMD-CC investigators took a new approach to this problem by tagging lymphocytes from birth to final disappearance from the bloodstream.

Radioactively labeled thymidine, a precursor substance of lymphocytes which is incorporated in the deoxyribonucleic acid (DNA) of newly dividing cells, was continuously infused into the rat until the last unlabeled cell disappeared. In this way, reutilization of fragments of cells born prior to infusion does not affect the lifespan estimate which was indicated by the disappearance of unlabeled cells.

Drs. J. R. Little, George Brecher, S. Rose, and T. R. Bradley, NCI visiting scientists from the University of Melbourne, Australia, indicate that the long lifespan of the small lymphocyte may be of great functional significance since recent studies by them and other investigators strongly suggest that this lymphocyte is capable of dividing and transforming into antibody-forming cells. The scientists believe that the continuous availability of such cells capable of going to sites of antigenic stimulation where they can "set up business" and provide local antibody responses make possible new hypotheses for further experiments on the kinetics and functional potentialities of the small lymphocyte. Their work is reported in *Blood*.

RAPID AND SENSITIVE METHOD TO DETECT NARCOTICS, BARBITURATES, CERTAIN OTHER DRUGS IN URINE

NIAMD scientists have developed an unusually sensitive and rapid method of detecting and identifying narcotics, barbiturates, and phenothiazines in the urine of patients. The procedure promises to be a valuable tool in toxicology, forensic medicine and study of the metabolism and mode of action of these drugs.

One of the major areas of research on addiction and drug abuse is the development of new methods to detect drugs in the body. Nalline, a morphine antagonist, is sometimes used to detect dependence on drugs, but the nalline test is not quantitative and has other limitations. The use of paper chromatography has distinct disadvantages in forensic medicine and toxicology because of the 12 to 20 hours needed for chromatogram development, and because of the inability to separate certain closely related compounds.

In order to facilitate studies now being undertaken in many large cities of recidivism in paroled narcotic addicts, the NIAMD scientists studied the applicability of thin-layer chromatography to the analysis of narcotics in the urine. This technique which permits the rapid separation of various organic compounds employs glass plates coated with absorbent material.

Use of this technique has permitted the detection of 5 to 10 micrograms of these drugs or their metabolites in a period of 4 to 5 hours.

Closely related compounds such as morphine and nonmorphine which are difficult to separate with paper, have been easily separated with thin-layer chromatography. Other investigators have used the NIAMD method to study *in vitro* metabolism of the analgesic, propoxyphene, to obtain metabolite separation not possible with paper.

The NIAMD scientists, Drs. Joseph Cochin and John W. Daly, have reported at a meeting of the American Society for Pharmacology and in *Experientia*, volume 18, that thin-layer chromatography can also be adapted for *in vitro* and *in vivo* studies of analgesics, barbiturates, and phenothiazines.

STUDY OF FEMALE SEX HORMONE METABOLISM DISCLOSES DIFFERENT METABOLIC PATHWAYS IN INFANT, ADULT

Extensive studies of fetal metabolism over a 5-year period have led Swedish grantees of NIAMD to suggest that estrogen excretion patterns which are normal in adults should perhaps be considered pathological when found in newborns or infants.

Analysis of the distribution and metabolism of female sex hormones by healthy human fetuses disclosed that the fetus is capable of metabolizing estrogen by the third month of pregnancy and that, unlike adults, the active products of this metabolism can be completely disposed of by the fetus or infant.

In human pregnancy, a dozen or more estrogens produced by the placenta are excreted in the urine. It has been generally assumed that the highly active estrogens, estradiol, estrone and the less active estriol are the primary hormones elaborated by the placenta. It has been known that the conversion of the active estrogens to the less active estriol form generally takes place in the liver.

Dr. Egon Diczfalussy of Karolinska Sjukhuset, Stockholm, Sweden, has proposed a scheme of estrogen metabolism involving hydroxylation of estradiol to highly polar, polyhydroxylated products. Based on his data, the investigator suggested that these metabolites, while lacking estrogenic activity, might stimulate certain aspects of fetal growth and development.

In discussing the significance of these studies, the grantee suggested that the metabolic system he has worked out may constitute a mechanism to defend the fetus against the high estrogenic and progestational hormonal activity of its maternal environment. In addition, the deviating pattern of estrogen excretion in cases of mongolism found by these investigators and the considerable amounts of estrone and estradiol in newborns suffering from congenital dislocations of the hip reported by others, led the author to suggest further that an estrogen excretion pattern which is normal in adults should perhaps be considered pathological when observed in newborns or infants.

Dr. Diczfalussy and his associates reported their studies in *Endocrinologiae Progressus* and *Recent Progress in Hormone Research*, volume 17.

STUDY OF SQUID EYES HELPS EXPLAIN CONVERSION OF LIGHT INTO NERVE IMPULSES

NIAMD scientists studying the chain of events connecting light absorption by the retina with the production of electrical nerve impulses to the brain have found that squid rod cells—like ordinary nerve cells—behave as miniature telegraph cables. This finding, obtained by using a new method for positioning electrodes in living slices of retina, clarifies the physiological mechanism of light sensitivity in the retina.

The sensitivity of the human retina to light depends, in part, on the presence of a purple photopigment, rhodopsin or "visual purple," in the rod cells. When a photon of light is absorbed by any molecule of rhodopsin, in a dark-adapted human retinal rod cell, the cell sends a sensory message to the nervous system. Though the efficiency of human photoreceptors has long been known, the excitatory mechanism connecting photopigment molecules to the sensory output is unclear; hypotheses are that either the photon absorption releases molecules which then diffuse along the cell until they reach a spot where nerve impulses can be generated, or that photon absorption creates a pair of charged particles which diffuse independently until reaching an impulse-generating area.

In order to study this problem, the scientists devised a method of inserting microelectrodes in living slices of retina and stimulating regions of the slices with small spots of light. (The squid retina's simplicity and lack of nonphotoreceptor cells make possible experiments difficult or impossible with other retinas.) The precise positions of these electrodes, light spots and photoreceptor cells were observed by means of an infrared microscope with an attached image converter tube. It was necessary to do the work under infrared light to preserve the dark adaptation of the squid retinal cells.

The investigators found that light produces some local electrical change in the photopigment-bearing process or outer segment of the squid rod which allows an inward positive current to flow through the cell membrane at points where photons are actually being absorbed at any given moment. The effect of this current is to transmit a signal rapidly along the photoreceptor to distant points where nerve impulses may be generated.

The scientists, Drs. W. A. Hagins and Ralph G. Adams of NIAMD's Laboratory of Physical Biology, and H. V. Zonana of Johns Hopkins University Medical Center, conclude that the excitatory mechanism is a depolarization of the whole photoreceptor by a flow of membrane current through only that part of the cell which is illuminated. Their work, which may help to explain the related problem of energy absorption in photosynthesis and cellular metabolism in general, is reported in the *Journal of General Physiology*.

HIGH DEGREE OF MOLECULAR ORIENTATION OBSERVED IN LIVING CELL

NIAMD scientists studying energy transfer mechanisms and allied metabolic steps have demonstrated the marked orientation of a species of chlorophyll molecules within a chloroplast (plant intracellular bodies containing the major photosynthetic pigment, chlorophyll). This finding, obtained by examining microscopically the fluorescent emissions of chloroplasts may shed light on the essential process of photosynthesis—how light energy is trapped and converted to chemical energy needed for the synthesis of sugar and other substances.

The investigators, Drs. Rodney A. Olson and William H. Jennings of NIAMD's Laboratory of Physical Biology, and Warren L. Butler of the Department of Agriculture, found that the fluorescent infrared radiation emitted by a single chloroplast was highly polarized. This means that for one species of chlorophyll nearly all the molecules are aligned in the same direction, and seem ideally situated to serve as the active centers of photosynthetic activity. Other species of chlorophyll do not show this emission and appear not to be oriented.

This finding, reported in *Biochimica Et Biophysica Acta*, suggests that the oriented form of chlorophyll may be involved in the transition from a physical mechanism of energy transfer to a chemical one. This study may also lead to a better interpretation of such mechanisms in all living cells.

MANNER OF ADMINISTRATION OF RADIOISOTOPE SHOWN TO BE MOST IMPORTANT FACTOR IN DETERMINING RADIATION EXPOSURE

Dr. John Z. Hearon, Office of Mathematical Research, NIAMD, has shown that the rate and method by which radioactive material is administered to the body are more important than the measurable amount of radioactivity within

the body when calculating radiation exposure or possible damage due to exposure. Although Dr. Hearon's general law has immediate application in the determination of permissible levels of radiation exposure for people or animals in a radiation environment or research study, its greatest usefulness to future research may live in the area of assessment of the effects of drug administration.

It has been generally accepted that the total radioactive count in the body at a particular time, the so-called body burden, was the most important indication of the amount of radiation received by body tissues. As a result of Dr. Hearon's studies it is now established that for a given body burden the rate of administration of the radioactive material determines the dose of radiation received by the body tissues. In essence, the more rapid the rate of administration the greater the dose of radiation received.

The work was reported in Health Physics.

NATURE OF BIOSYNTHESIS OF THYROID HORMONAL SUBSTANCE REVEALED

Studies by NIAMD scientists have shown that an enzyme in rattlesnake venom, L-amino acid oxidase, is capable of converting a known thyroxine-precursor into thyroxine, indicating that a substance identical to that formed by this enzyme may be the missing link necessary for thyroxine synthesis. In addition, use of the enzyme provides a simple method for synthesis of this important hormonal substance, the active hormone of the thyroid gland necessary for regulation of energy-releasing processes in all body tissues.

Although thyroxine has been synthesized long ago in the test tube for therapeutic and research purposes, the process by which the thyroid gland forms this substance is unknown. Specifically, thyroxine is known to be formed from diiodotyrosine (DIT), a naturally occurring, iodine-containing amino acid, but the mechanism of conversion of DIT into thyroxine has been unclear.

The NIAMD scientists have now found that small amounts of L-amino acid oxidase can convert DIT into thyroxine in the test tube. The enzyme oxidizes DIT to a compound which is no longer an amino acid but a keto acid (keto acids are agents which serve as intermediates in a variety of metabolic processes). As soon as this keto acid, 4-hydroxy-3,5-diiodophenylpyruvic acid (DIHPPA), is formed, it combines with DIT that had not yet been attacked by the enzyme, resulting in the formation of thyroxine.

Although the presence of DIHPPA in the thyroid has not yet been shown, this experiment suggests that thyroxine synthesis in the gland may proceed via DIHPPA, thus implicating this keto acid as the missing link in the conversion mechanism.

Aside from the possible biological significance resulting from this study, the process is of great practical importance, since it is the simplest known method for the synthesis of thyroxine and particularly of radioactively labeled thyroxine which, in turn, is an important research tool. The study, by Drs. H. J. Cahnmann and Tetsuo Shiba, is reported in the 1962 Abstracts of the Federation of American Societies for Experimental Biology.

ORGANIC BUFFER THAM USEFUL IN TREATMENT OF CARBON DIOXIDE INTOXICATION

NIAMR grantees have reported encouraging results following the administration of the organic carbon dioxide buffer THAM (2-amino-2-hydroxymethyl-1,3-propanediol) to patients with carbon dioxide intoxication and with excessive blood CO₂ (hypercapnia), syndromes arising from chronic lung disease and other disorders impairing ventilation. The study indicates that the drug is a useful adjunct in the treatment of severe CO₂ intoxication when other therapy is not successful or rapid enough to combat retention of the gas.

Successful treatment of respiratory acidosis (decreased plasma pH resulting from CO₂ retention and hypercapnia) depends on mechanical respirators and other therapy to improve ventilation. Occasionally, treatment cannot be rapid enough to prevent death; in this circumstance an agent might buffer the acidotic blood with an alkaline solution to allow sufficient time for specific therapy to rid the body of excess CO₂. Buffers such as sodium bicarbonate and sodium lactate have the disadvantage of requiring moderately large fluid infusion with

high sodium content. Recently, the buffer, THAM, had been reported capable of preventing hypercapnia in dogs with greatly reduced ventilation. In order to evaluate the effectiveness of the drug in respiratory acidosis, the NIAMD grantees administered it to nine patients with severe CO₂ intoxication and with moderate hypercapnia without overt neurological or circulatory manifestations.

Infusions of THAM were given to the patients, and various determinations, including the analysis of blood samples for oxygen, carbon dioxide content and pH, were made. Among other findings it was shown that optimal results—an increase in arterial pH and a fall in carbon dioxide tension—were obtained when THAM was administered along with the use of mechanical respirators. The results also indicated that THAM should not be administered unless ventilation is assisted by a respirator. Eight of the patients showed complete clinical recovery within several days to 4 weeks.

THAM is produced by Abbott Laboratories, North Chicago, Ill.

The NIAMD-supported investigators, Drs. H. O. Sieker and his associates at Duke University Medical Center, Durham, N.C., also found that the administration of THAM to six control subjects had a variable response but, in general, tended to increase ventilation. Their work appeared in the *Annals of the New York Academy of Sciences*.

OXYGEN METABOLISM IN LIVER CLARIFIED

Studies of oxygen metabolism in the liver by NIAMD grantees have shown that the liver accounts for approximately one-fifth of the total human oxygen consumption in health. Their studies, involving normal subjects and patients with liver cirrhosis, also indicate that the standard sulfobromophthalein (BSP) liver function test may provide a sensitive index of the presence of liver hypoxia and the effectiveness of oxygen inhalation therapy in correcting this oxygen deficiency.

Liver hypoxia is often present in heart failure, shock, liver disease, and following exercise, and it may lead to inhibition of vital enzymatic functions. Although oxygen therapy has been used clinically in states of impaired liver function, it has not been possible to assess its effectiveness objectively.

Studies using the newly available dye, indocyanine green, to measure hepatic blood flow have shown that the BSP test can be used as a sensitive index of liver hypoxia. This test involves the injection of BSP and measurement of its rate of removal from blood; abnormal retention indicates liver dysfunction. Hepatic oxygen consumption was determined by multiplying arterial-hepatic vein oxygen difference by hepatic blood flow.

The grantees found that liver dysfunction, as reflected in abnormal hepatic uptake of BSP, occurs when there is inadequate oxygen to fulfill tissue needs. Apparently, adequate oxygenation is necessary for uptake, conjugation, and excretion of this dye. Therefore, the rate of removal of BSP may provide a sensitive index of hypoxia.

The NIAMD grantees, Drs. C. M. Leevy, Wm. George, and their associates at the Seton Hall College of Medicine and Jersey City Medical Center, N.J., have also confirmed the effectiveness of oxygen inhalation in improving BSP removal capacity in selected patients with chronic liver disease. Further studies are underway to determine the value of oxygen therapy in preventing major structural changes of the liver in hypoxia and in facilitating regeneration in patients with chronic active hepatic disease. Their report was published in the *Journal of the American Medical Association*.

ALLERGY AND INFECTIOUS DISEASE ACTIVITIES

THURSDAY, MARCH 14, 1963.

WITNESSES

DR. JUSTIN M. ANDREWS, DIRECTOR, NATIONAL INSTITUTE OF
ALLERGY AND INFECTIOUS DISEASESDR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF
HEALTHKENNETH H. BROWN, EXECUTIVE OFFICER, NATIONAL INSTITUTE
OF ALLERGY AND INFECTIOUS DISEASESB. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL
INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	3,796	4,515	4,680
Positions other than permanent.....	45	46	46
Other personnel compensation.....	101	127	162
Total personnel compensation.....	3,942	4,688	4,888
12 Personnel benefits.....	467	500	550
21 Travel and transportation of persons.....	175	271	271
22 Transportation of things.....	72	67	67
23 Rent, communications, and utilities.....	98	89	128
24 Printing and reproduction.....	8	10	10
25 Other services.....	2,563	5,549	5,765
Payment to the National Institutes of Health man- agement fund.....	3,810	4,332	4,504
26 Supplies and materials.....	831	951	969
31 Equipment.....	524	466	404
41 Grants, subsidies, and contributions.....	40,802	47,747	51,678
Subtotal.....	53,292	64,670	69,234
Deduct quarters and subsistence charges.....	6	8	8
Total obligations.....	53,286	64,662	69,226

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	644	700	710
Full-time equivalent of other positions.....	7	7	7
Average number of all employees.....	617	677	702
Number of employees at end of year.....	647	708	708
Average GS grade.....	6.6	7.0	7.0
Average GS salary.....	\$6,001	\$6,456	\$6,600
Average salary of ungraded positions.....	\$4,444	\$4,855	\$4,621

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	33,517	37,647	40,628
(b) Fellowships.....	1,810	2,900	3,058
(c) Training.....	5,475	7,200	7,992
Total, grants.....	40,802	47,747	51,678
2. Direct operations:			
(a) Research.....	9,309	10,534	10,981
(b) Collaborative studies.....	1,071	5,029	5,284
(c) Review and approval of grants.....	656	857	992
(d) Program direction.....	280	403	291
(e) Rocky Mountain Laboratory facility.....	598	92	-----
Total direct operations.....	11,914	16,915	17,548
Total program costs, funded ¹	52,716	64,662	69,226
Change in selected resources ²	570	-----	-----
Total obligations.....	53,286	64,662	69,226
Financing:			
Comparative transfers to other accounts.....	1,373	1,547	-----
Unobligated balance brought forward.....	-----	-92	-----
Unobligated balance carried forward.....	92	-----	-----
Unobligated balance lapsing.....	1,323	16	-----
New obligational authority.....	56,074	66,133	69,226
New obligational authority:			
Appropriation.....	56,091	66,142	69,226
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728 (-)).....	-17	-9	-----
Appropriation (adjusted).....	56,074	66,133	69,226

¹ Includes capital outlay as follows: 1962, \$358,000; 1963, \$466,000; 1964, \$404,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$297,000 (1962 adjustments, \$626,000); 1962, \$1,493,000; 1963, \$1,493,000; 1964, \$1,493,000.*Personnel summary*

Mr. FOGARTY. Dr. Andrews, I believe you are next. Put in your full statement, in the record, Doctor, and you may summarize it.

Dr. ANDREWS. Yes, sir.

(The statement follows:)

Mr. Chairman and members of the committee, the National Institute of Allergy and Infectious Diseases recently held a 1-day meeting to celebrate the 75th anniversary of infectious disease research in the Public Health Service. The participation of the chairman of this committee was appreciated. The occasion provided some interesting and challenging perspectives of progress in microbiological research.

The implication of new findings, together with an advanced technology that permits us to explore promising leads, underlie our new opportunities. The finding in animals that viruses cause cancers and set the stage for chronic disorders of the nervous system opens important areas for research. The Institute's Laboratory of Infectious Diseases, conducting extensive studies of cancer-causing viruses, has implicated types of adenovirus (agents usually associated with diseases of the upper respiratory tract in humans) in cancer of hamsters. At the Rocky Mountain Laboratory, Hamilton, Mont., research is underway on scrapie and other chronic virus infections of animals, in the hope that these diseases will provide comparisons with human illnesses.

The Institute continues to move forward in traditional areas of infectious disease research. Country after country is being freed of malaria in eradication efforts aided by our malaria work and sponsored by the World Health Organization. We are accustomed to think today in terms of broad-scale disease pre-

vention and disease eradication. Thus, research by the National Institute of Allergy and Infectious Diseases seeks vaccines to prevent numerous diseases. New or improved vaccines against cholera, Colorado tick fever, mosquito-borne encephalitis, and other infections are now at the phase of initial tests in volunteers.

The capacity of the Institute for research has increased greatly in terms of men and material. New means of collaboration, of Government-university-industry teamwork are being evolved. The vaccine development program against the viral pneumonias and other infections of the upper respiratory tract is an example of a collaborative program that should expand our national capacity to develop and produce new vaccines. A new insectary, being put into operation at the Rocky Mountain Laboratory, will increase resources for the study of insect-borne diseases such as viral encephalitis. A pilot data-processing unit is being established in the Institute to enable better reporting about some 2,000 research grants and other extramural programs, a vital step toward improvement of communications to all pertinent audiences.

VIRUS DISEASES AND VACCINE DEVELOPMENT

Research on the cause and cure of virus diseases continues to command the interest of our scientists and grantees, with strong emphasis on the many problems posed by the ubiquitous respiratory viruses.

Scientists have moved beyond the point of debating whether viruses can be a cause of chronic illnesses. Rather they are now concerned with the extent to which viruses are involved in the neurologic diseases, and in heart ailments and cancer, to name a few of the broad areas where viral causation and complication are being vigorously explored. In this search, Institute virologists are playing a leading role.

The vaccine development program under this Institute's aegis has now been underway for a year. Focusing on the agents known to cause a majority of serious respiratory illnesses, the program aims at the production of prototype vaccines against respiratory syncytial virus, parainfluenza viruses, Eaton agent (pleuropneumonia-like organisms), and some of the adenoviruses. Six contracts have been awarded to commercial firms interested in developing prototype vaccines, and four contracts have been negotiated for clinical evaluation of the new vaccines as they become available. Additional contracts are in prospect.

This year saw the first of what hopefully may become a biennial event, the 3-day conference on newer respiratory disease viruses. The meeting featured 37 participants, of whom 9 were NIH scientists, and 15 were grantees of NIAID. The conference was made possible by an NIAID grant to the University of Southern California School of Medicine. The published proceedings of the conference will bring together in a single volume the vast amount of contemporary information available concerning the viruses presently known to be associated with respiratory diseases.

One of the reports from the conference described investigations of viral infection in volunteers. Over the past 2½ years, more than 500 volunteers have been experimentally infected with a variety of viruses given under stringently controlled conditions at the clinical center of the National Institutes of Health.

A problem in these studies has been lack of knowledge about how artificial inoculation compares with infection as it occurs in nature. One approach in the simulation of natural conditions of infections has been to infect volunteers with known amounts of virus dispersed by means of small particle aerosols. A variety of aerosol dosages is under study to determine whether different dosages of the same virus produce illnesses with dissimilar symptoms.

Cure, or even significant amelioration, of the illnesses caused by respiratory viruses remains at this time an earnestly sought goal worthy of the widest variety of approaches. Clues to the conquest or containment of these illnesses will surely be found in the scientific data which has been accumulating so rapidly during the last decade and to which NIAID scientists have made notable contributions.

Another problem of vaccination, the protection of groups at special risk because of serious illness, was investigated by grantees of NIAID. Two groups of investigators studied the effects of measles vaccine in children with cystic fibrosis and with leukemia in whom concurrent measles would present an unusual danger. Of more than 200 children with cystic fibrosis, 75 had no unfavorable reaction to attenuated measles virus vaccine. Reactions in a small group of

acutely leukemic children led the investigators to conclude that at this time administration of the vaccine is contraindicated in cases of leukemia.

Two aspects of a viral problem, rabies in bats, have been brought into focus by a 7-year study of bats in Montana. One is the actual and potential spread to humans of this invariably fatal disease; the second is the transmission of the virus to wild animals and livestock. Since 1954, investigators at the Rocky Mountain Laboratory have examined bats of almost all species known in Montana and have demonstrated rabies virus in 21 bats of 8 species. Six cases of human rabies in this country have been attributed directly to bats, and the increase of rabid bats constitutes a potential public health problem of major import.

EATON AGENT, THE PLEUROPNEUMONIALIKE ORGANISM OF PRIMARY ATYPICAL PNEUMONIA

Still another respiratory disease agent—neither a virus nor a true bacterium—is being studied in human volunteers at the clinical center. This is Eaton agent, the pleuopneumonia-like organism (PPLO) discovered last year by Institute scientists to be the first of its kind known to cause human illness, specifically primary atypical pneumonia. Clinical studies of this agent in volunteer patients are providing convincing confirmation that the Eaton PPLO can cause respiratory disease in man, ranging from mild upper respiratory involvement to pneumonia.

Based on what they now know about Eaton PPLO and its relation to respiratory disease, scientists are speculating that these organisms may play a role in other, still undefined, human respiratory illnesses.

Much work remains to be done before the PPLO's can be understood as well as we now understand bacteria and viruses. Basic investigations are already underway in the Institute to improve means of cultivating and identifying the organisms. Studies of these agents in depth may furnish answers to some of the pressing practical problems which have presented themselves along with the knowledge that PPLO's are important in human disease.

VIRUS REAGENTS PROGRAM

In the vital area of virology, the basic reagents used in critical experiments by hundreds of virologists generally have been put together in individual laboratories with little assurance of comparability. The National Institute of Allergy and Infectious Diseases reported to this committee last year on the establishment in October 1961 of the virus reagents program, representing a combining and unification of several NIH activities.

Nine contracts in total amount of \$1½ million have now been awarded for production of virus reagents and for certification by independent testing agencies. Storage and distribution facilities have been established.

The reagents include both viral antigens to stimulate biological reactions and antisera containing the antibodies specific to these viruses. These materials are vital to identifying viruses and understanding virus diseases.

Antigens and antisera produced by numerous types of adenoviruses, enteroviruses, and respiratory agents such as influenza and parainfluenza have been made and are being packaged. We expect these reference materials will soon be available to qualified researchers of NIH and elsewhere.

Arrangements are in progress for endorsement of the preparations by the World Health Organization as international reference reagents. Thus, we hope that a mechanism will be established to provide comparability of results obtained by virus laboratories throughout the world.

ALLERGY-IMMUNOLOGY

Millions of allergic individuals find only partial or emergency relief for hay fever, asthma, allergic skin disease, allergic headache, drug reactions, and other manifestations of hypersensitivity. As the precise causes of allergy are not known, most research is fundamental. In the Institute this research is conducted in the laboratory of immunology at Bethesda; at the Rocky Mountain Laboratory, Hamilton, Mont.; and through some 300 grant-supported investigations.

The scientific discipline of immunology holds the key to allergy. Thus, to head this program the Institute has recently been fortunate in recruiting one of the world's foremost immunologists, Dr. Maurice Landy.

The program of the laboratory of immunology also pervades the clinical field through collaboration of clinical associates of the laboratory of clinical investigation and through weekly immunology seminars held during the academic year. These meetings are regularly attended by some 300 clinicians and bench scientists who thus gain an understanding of this basic, important, but relatively new discipline. A member of the staff of the laboratory of immunology recently served as an expert consultant to the World Health Organization, which sought advice in establishing an immunology research program.

The laboratory is continuing its investigations concerning a type of thyroiditis suspected of being a disease of autoallergy—that is, a disease due to an individual's hypersensitivity to substances produced within his own body. In the guinea pig, delayed skin reactivity has been found consistently and closely to parallel experimental allergic thyroiditis during its developmental and declining phases; it may, therefore, be a clue to the nature of the disease in man.

Many facets of allergy are being explored through the program of research grants. Grantees at the University of Cincinnati College of Medicine recently conducted immunoelectrophoretic tests of serum specimens from 1,618 infants, most of them ill. After clinical studies of some of these infants, the investigators correlated precipitins to native milk proteins with certain undifferentiated illnesses. They believe the serum tests provide a rapid means for identifying in infants ill with milk allergy so that certain milk proteins may be removed from their diet.

In another grant-supported study, investigators at the University of Pennsylvania School of Medicine described means they have developed for protecting workers against chromium dermatitis in industry. A number of investigations of the important allergic skin diseases comprise an important segment of research on hypersensitivity. Extensive research on airborne allergens is also underway.

PARASITIC DISEASES

The Institute's competence in parasitic disease research is a rich resource which grows in importance with our country's deep involvement in world health problems. The global importance of tropical health is underscored in the recent summary report of the National Research Council, which defines the tropics as an area in which approximately half the population of the world resides and which comprises most of the economically underdeveloped regions now in great ferment in the search for a better life. The value of research contributions to better international health is nonetheless real for being virtually incalculable. Institute scientists have long been sought for advice on world health problems. A new activity this year was intensive instruction specifically oriented to the needs of Peace Corps volunteers and to surgical teams sent from the United States to tropical countries.

One of the exciting accomplishments of the past year has been the finding of a new, long-lasting antimalarial drug, still experimental, which after a single injection has continued for a year to protect human volunteers from malaria induced by heavily infected mosquitoes. This new drug, CI-501, developed by scientists at Parke, Davis & Co., was furnished to Institute scientists for clinical study. Results to date are termed spectacular by some malaria investigators. Thus far the drug has been protective nearly 10 times longer than conventional drugs now used to suppress the disease.

Fifty prisoner volunteers participated in the study. They were bitten by infected mosquitoes varying numbers of times, but none has developed clinical or parasitological evidence of malaria. Other volunteers serving as controls without drug invariably came down with malaria promptly when bitten by the same mosquitoes.

The drug has also been used experimentally to cure established cases of malaria and has apparently effected cure as evidenced by disappearance of symptoms. Institute investigators believe that more studies will have to be undertaken before it will be known if the drug is actually curative as well as protective. It is possible that this new antimalarial eliminates the parasites before infection becomes established.

If these findings, which we regard as only preliminary, are borne out under actual field conditions in malarious areas of the world, the malaria-eradication program of the World Health Organization, supported to a large degree by this country, will have a potent new weapon with which to fight malaria.

It is clear from mounting evidence that new, effective drugs are an urgent necessity if the campaign to eradicate the disease is to succeed. After last year's

disclosure of the ineffectiveness of chloroquine against one strain of the disease, further studies were begun. It has now been found that other strains from widely separated areas of the world show resistance to some, and in some cases to practically all, of the synthetic drugs. Now scientists have found that not only do chloroquine and amodiaquine and other antimalarials fail to cure malaria in certain parts of the world but that they also are ineffective in suppressing the infection. The loss of chloroquine and similar drugs as reliable antimalarials, after years of demonstrated usefulness dating back to World War II, may become a serious problem, especially for our Armed Forces. The specter of resistance makes new, potent drugs doubly welcome at this time.

Research on simian malaria and its relation to the human disease continues in Malaya where the Institute's field group, the Far East research project, is working in an area of high malaria endemicity. Four species of simian malaria, including one new to science, have been isolated from mosquitoes caught in the wild. Studies in Malaya have proved that one mosquito species, *Anopheles balabacensis introlatus*, is a vector of simian malaria and that this species attacks man as readily as monkeys.

Schistosomiasis is another parasitic disease of worldwide importance which our scientists are studying. Paradoxically, modern irrigation systems are opening the way for the spread of this fresh-water snail-borne disease which afflicts millions in the Middle East, Africa, Asia, and Latin America. Control of schistosomiasis conceivably would be effective if there were available a mass treatment drug that would sterilize adult worms even if it did not produce definitive cure. A pilot study to test this thesis has been started in Egypt, featuring infrequent administration of low dosages of antimony-containing drugs.

In addition to the field work in collaboration with medical authorities in Egypt, basic laboratory studies in Bethesda on the biology and control of snail intermediate hosts of schistosomes are continuing. Studies are also underway on the efficacy of the antimony-containing drugs against the parasites that cause the disease.

BACTERIAL DISEASES

Grantees at the Johns Hopkins Hospital reported this year a change in the type of staphylococcus causing the majority of infections in hospitalized patients. Investigators found that type 54 replaced type 80/81 as the most common strain. They correlated the finding with an increase in use of a particular antibiotic in surgery. Their data indicated that this was the factor that caused type 54 staphylococci to become virulent for surgical patients. Their observations also led them to conclude that, fortunately, type 54 may be a lesser threat to healthy adults than type 80/81.

This year for the first time scientists of the Institute have observed directly the growth of the cell wall of the bacterium *Streptococcus pyogenes*. In the past, information about cell-wall synthesis has been obtained indirectly and retrospectively. Now, by the use of immunofluorescent methods, it is actually possible to see the growing bacterium. Observations suggest that cell-wall synthesis occur simultaneously in at least two sites. The scientists found that growth begins at the Equator of the organism and then extends both inward and to the surface. Although this pattern is known to apply only to the single species observed, the investigators' methods should be widely applicable to the observation of other bacteria.

Two bacterial diseases which still present grave problems of clinical management are subacute bacterial endocarditis and urinary-tract infections. A new bacterium currently designated by the Communicable Disease Center as group II-D has been implicated as a previously unrecognized cause of subacute bacterial endocarditis, a prolonged, febrile disease which is often fatal. Investigators from the Universities of Florida and Alabama report four cases found over a wide geographic area within 10 months. They suggest that this widespread organism is the cause of endocarditis in a small but significant number of cases.

Stubborn urinary-tract infections, requiring long treatment with antibiotics, often present the further complication of drug resistance. An Institute grantee at the Upstate Medical Center, New York, is investigating the possible effect of urine acidity on the effectiveness of some of the newly developed antibacterial agents. Adjustment of pH in urine may be an important way to enhance antibacterial activity and thereby permit more effective treatment of this widespread condition, which if left unchecked leads to severe, permanent kidney damage.

MIDDLE AMERICA RESEARCH UNIT

The middle America research unit in the Panama Canal Zone, cosponsored by the Walter Reed Army Institute of Research, is the field facility of this Institute's Laboratory of Tropical Virology. It is one of several centers for medical investigations of health problems of importance to people in the American tropics and certain areas of the United States. Primary emphasis is on fungus diseases, such as histoplasmosis, and on arthropod-borne viral infections.

During a recent epidemic of Venezuelan equine encephalitis in the area, three MARU staff members contracted the disease and another, who had previously received experimental encephalitis vaccine, acquired laboratory infection with VEE virus. Studies of these illnesses have provided new data on this disease, which resembles the encephalitides epidemic from time to time in various areas of the United States.

The middle America research unit cooperated in epidemiologic and laboratory studies in an outbreak of illness at Fort Kobbe, confirmed as leptospirosis, the first record of this infection in Panama, and also helped investigate salmonellosis and other diseases among military and civilian personnel and persons indigenous to the area.

The Laboratory is studying Indiana-type vesicular stomatitis virus, Cache Valley virus, sandfly virus, tick fever, various respiratory viruses, Eastern and St. Louis equine encephalitis, Ilheus virus, and others. Frequently, frozen specimens are air-expressed to the Bethesda laboratories for further investigation.

The middle America research unit is also participating in epidemiologic studies in Bolivia of a hemorrhagic fever of unknown etiology. Over 500 endemic cases with high mortality have occurred in an isolated area of northeast Bolivia during the last 3 years.

GORGAS MEMORIAL LABORATORY

The Gorgas Memorial Laboratory, the functional unit of the Gorgas Memorial Institute of Tropical and Preventive Medicine, was established in the Republic of Panama in 1929, with the support of the Governments of the United States and Panama, and has been continuously active in medical research since that time.

Located on the Isthmus of Panama, a crossroads of the world, the Gorgas Laboratory is in a position to take advantage of many rich opportunities for research. The staff is composed of members known throughout the world for their accomplishments in advancing the medicine of the tropics, a category of growing importance to the health of the Americas. The additional laboratory space provided through recent congressional appropriation will greatly facilitate studies underway and planned.

The decision of the Inter-American Highway Commission to construct that portion of the Inter-American Highway which will traverse sparsely inhabited areas (Darien Gap) of the jungle in eastern Panama has focused the attention of the Gorgas Laboratory on this area. The etiologic agents of Venezuelan equine encephalitis, St. Louis encephalitis, vesicular stomatitis, American cutaneous leishmaniasis, and American trypanosomiasis have been recovered by Gorgas investigators during the past 10 years from similar portions of the Panamanian rain forest. With the new road project, the vast eastern part of Panama will be transformed into a natural laboratory for the study of medical ecology. The Department of Public Health of Panama has given the Gorgas Laboratory responsibility for conduct of medical surveillance aspects of the Darien Gap project. A complete profile study is being taken on 200 engineers and crewmen who will begin surveying the route of the highway. The men will serve as sentinels in the medical sense. At the same time, they will be protected by constant observation to prevent duplication of the loss of lives experienced in building the Panama Canal. In concurrent studies, observations will be made of the Indian and Negro tribes living in the Darien Gap to watch the effects of introducing these people to Western civilization. After the initial 4-year period devoted to basic surveys, baselines will be established for specific research studies in depth.

This is but one example of a number of investigations underway at the Gorgas Laboratory. Studies of vesicular stomatitis, leishmaniasis, malaria, Chagas' disease, and other infections important in the Americas to man and domestic animals are being continued.

Through the cooperation of the U.S. Wildlife Service, several thousand bands have been obtained in order to band migratory birds of the area. Because thrushes are abundant near the Laboratory and because at least one species is important as a host of Eastern equine encephalitis virus in the Eastern United States thousands of thrushes will be studied. Blood samples are being taken from many kinds of migratory birds to test for viruses transmissible to man through the bird-mosquito-man cycle.

Maj. Gen. Paul H. Streit (U.S. Army, retired), President of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., has submitted a copy of the operating budget for the Gorgas Memorial Laboratory. As spokesman for the Gorgas Institute before Congress, I am requesting that the maximum funds authorized by Congress, amounting to \$250,000, be made available to the Institute during the 1964 fiscal year.

ROCKY MOUNTAIN LABORATORY

In the years since Rocky Mountain spotted fever vaccine was developed there, the Rocky Mountain Laboratory at Hamilton, Mont., has achieved world eminence for its research on diseases common to lower animals and humans. Today a vaccine against Colorado tick fever is used experimentally in human volunteers with no toxic reactions and with promising antibody titres. Studies of bat rabies, overwintering mechanisms of encephalitis virus, Q-fever, and other problems are underway. A new insectary will increase the capacity of the Rocky Mountain Laboratory for research on insect-borne viruses. Long-term studies of larger animals are proposed when facilities to house them become available. Studies of comparative pathology can then be extended.

In the new project in comparative pathology, the phenomenon of chronic viral infection, as exemplified by three natural diseases of animals, is being investigated to provide some insight into pathogenic mechanisms which may be involved in certain chronic infectious diseases of man. To date the study has been limited to exploratory work on scrapie in mice, although studies on Aleutian disease of mink and chronic pneumonitis of sheep are planned.

The possible role of viruses in causing slowly developing, protracted disease is almost impossible to study at present in man. Thus, the investigation of known chronic viral diseases of animals as laboratory models or prototypes is a logical first step in efforts to elucidate the general biologic phenomena involved. For example, the fact that scrapie virus can cause in animals a chronic neurologic disease progressing relentlessly to death after a prolonged incubation period is considered of fundamental importance to the understanding of disease in man. Studies of the scrapie virus are to be undertaken during the coming year.

The Rocky Mountain Laboratory is continuing its studies of cell fractions to obtain purified, more potent vaccine constituents. An apparatus for cell fractionation developed in this Laboratory is now being widely used by many research institutions.

SUMMARY

This report has provided a mere sampling of research progress. Continuous and impressive advances are being made through about 2,000 research grants and through some 200 Institute projects at Bethesda and field locations in Hamilton, Mont.; Columbia, S.C.; Hawaii; the Canal Zone, and Malaya.

It is apparent that much emphasis is placed on viral diseases. Basic work in this area is extensive. Technical advances in recent years, particularly the simplification of procedures for the culture of mammalian cells and the development of sensitive plaque assays for measuring virus infectivity, have provided new tools for the quantitative biochemical study of the replication of animal viruses. Studied from this point of view, viruses provide uniquely useful examples of rapidly reproducing, specific biological units, susceptible to investigation on the molecular level. Although specifically aimed at obtaining information on the biochemical basis for normal cell function through the use of viruses as tools, nevertheless most of the new knowledge obtained in these studies have implications for, or direct application to, practical problems involved in clinical disease caused by viruses.

Examples of additional studies underway in virologic and other fields include: evaluation of type III strain poliovirus vaccine in Yugoslavia; experiments in growing viruses in a continuous-flow, virus-synthesizing apparatus; observations on the cockroach as a carrier of hepatitis virus; fundamental

research into the mechanisms of fever, the age-old but never fully understood hallmark of disease; efforts to improve tuberculosis immunization; trials of a new mumps vaccine; research on postradiation susceptibility to infection; research on interferon, the antiviral substance; and trials of passive immunization of the pollen-sensitive individual. The morbidity and mortality statistics of future years on allergic and infectious diseases will reflect in terms of life-saving and reduced disability the gains of this impressive era of medical research accomplishments.

The 1964 request for the National Institute of Allergy and Infectious Diseases is \$69,226,000. This compares with an operating level of \$64,662,000 for 1963. The 1964 funds requested provide a net increase of \$3,931,000 for financing 142 additional research, fellowship, and training grants; \$447,000 for direct research; \$255,000 for collaborative studies; and \$135,000 for review and approval of grants. The request for 1964 is distributed among program activities as follows:

Grants and related contracts:

Research-----	\$40, 628, 000
Fellowships-----	3, 058, 000
Training-----	7, 992, 000
Subtotal, grants and related contracts-----	<u>51, 678, 000</u>

Direct operations:

Research-----	10, 981, 000
Collaborative studies-----	5, 284, 000
Review and approval of grants-----	992, 000
Administration-----	291, 000

Subtotal, direct operations-----	<u>17, 548, 000</u>
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Total 1964 request-----	<u>69, 226, 000</u>
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Dr. ANDREWS. Mr. Chairman and members of the committee, recently the National Institute of Allergy and Infectious Diseases marked the 75th anniversary of research on microbiology in the Public Health Service. The occasion enabled our scientists to review research progress since the days of Pasteur and thus to gain perspective on the myriad viral, rickettsial, bacterial, and fungal diseases which confront us today.

Armed with vastly improved techniques, equipment, and facilities, this Institute is currently pursuing answers to an ever-widening number of research problems. Two major collaborative efforts, employing the combined resources of Government, academic institutions, and industry, are aimed at providing means for development and production of new vaccines for the common cold and standardization of reference reagents for virus research. A number of contracts have been awarded for these purposes.

PAST YEAR ACCOMPLISHMENTS

Identification of the Eaton agent as a pleuropneumonia-like organism (PPLO) responsible for a variety of respiratory diseases gave new impetus to the clinical study of PPLO and related infectious agents in volunteer patients.

The first Conference on Newer Respiratory Disease Viruses, bringing together the leading scientists in the field, was supported by this Institute. Published proceedings of this meeting will make available the latest scientific information on this rapidly expanding research front.

Fundamental research in immunology contributed to a better understanding of hay fever, asthma, and other allergic diseases, includ-

ing hypersensitivity of infants to milk, autoallergy, and industrial and airborne allergies.

Institute parasitologists demonstrated in human volunteers that a new antimalarial drug (designated CI-501) developed by the pharmaceutical industry, offers protection for 1 year or longer from malaria infection from bites of malaria-infected mosquitoes. Resistance of malaria parasites to commonly used antimalarial drugs was found to be widespread, underscoring need for new chemotherapeutic agents useful in worldwide malaria-eradication campaigns.

Investigations of bacterial diseases uncovered a means for immunofluorescent study of cell-wall growth in streptococci. This method may also be applied to other bacteria. Research on *Staphylococcus*, other prevalent bacterial pathogens, and antibiotics also was advanced.

The Institute's Middle America Research Unit in the Panama Canal Zone continued its emphasis on the viral encephalitides and other infections of the American tropics.

The Rocky Mountain Laboratory in Hamilton, Mont., conducted extensive studies of diseases transmissible to man from lower animals and also pursued immunology research as a major program.

Recent significant accomplishments in tropical medicine research have been reported by the Gorgas Memorial Laboratory, Republic of Panama. As spokesman before the Congress for this laboratory, I request that funds in the amount of \$250,000 again be made available for its work.

INCREASE REQUESTED FOR 1964

The 1964 request for the National Institute of Allergy and Infectious Diseases totals \$69,226,000. This compares with an operating level of \$64,662,000 for 1963. The 1964 request will provide a net increase of \$3,931,000 for financing 142 additional research, fellowship, and training grants; \$447,000 for direct research; \$255,000 for collaborative studies; and \$135,000 for review and approval of grants.

Mr. FOGARTY. Thank you, Doctor.

The appropriation for 1963, adjusted for comparability, is \$64,678,000 and the request for 1964 is \$69,226,000, an increase of \$4,548,000.

RESERVE FOR SAVINGS

Now, you have a reserve for savings of \$16,000. Is that correct?

Mr. KELLY. That is correct.

Mr. FOGARTY. That is kind of a petty amount to put in the reserve.

Dr. ANDREWS. Yes, sir. This is a very small amount for that purpose.

Mr. FOGARTY. Is someone just trying to heckle you a little bit? That is a cut of less than three one-hundredths of 1 percent.

Mr. KELLY. This is a computation of an amount of lapse, which was considered to be appropriate on the new positions.

Mr. FOGARTY. Will you place in the record a table showing the reserve for savings for each Institute?

Mr. KELLY. Yes, sir.

(The requested table follows:)

Reserves for savings in operating appropriations of National Institutes of Health—Fiscal year 1963

	<i>Amount</i>
General research and services-----	\$332,000
National Cancer Institute-----	279, 000
National Heart Institute-----	1, 177, 000
Arthritis and metabolic disease activities-----	94, 000
Allergy and infectious disease activities-----	16, 000
Neurology and blindness activities-----	314, 000
Total-----	2, 212, 000

VACCINE FOR COLDS AND RESPIRATORY DISEASES

Mr. FOGARTY. Congress, and especially the Senate committee, has been after you to do more work on vaccine against colds and other respiratory diseases. I notice on page 50 you say:

The possibility of developing an effective vaccine against this multitude of agents begins to appear impractical.

Have you given up?

Dr. ANDREWS. No, sir.

Mr. FOGARTY. What does that mean? It is impractical?

Dr. ANDREWS. What is meant is that it is impractical to pursue by means of research grants. This is in the research grants section of the statement. This is why we have transferred vaccine development to the collaborative activities where we can do this work by contract, which is a much better method of providing specifications that we want built into the products to be tested for the common cold vaccine capability.

We do not feel that it is impractical to undertake to develop multiple-antigen vaccine for colds. We are aware that there will be many difficulties, many problems involved in developing effective vaccine but our hopes are undiminished in spite of this statement.

Mr. FOGARTY. It seems to me more people are having problems with their upper respiratory tracts in the last few years. Is it on the increase? This year, especially, everybody seems to have some kind of flu or cold.

Dr. ANDREWS. Well, we become very cognizant—

Mr. FOGARTY. And I hear more about people dying of pneumonia.

Dr. ANDREWS. We do become very cognizant of the common cold at this time of the year of course, and whether there is an actual increase—we are having a little flurry of influenza this year—I am not sure. My own impression is that the variation from one year to the next is usually not really very great.

Mr. FOGARTY. It seems to me everybody you meet this year has a cold, which they could not shake for weeks.

Dr. ANDREWS. May I tell you something about developments in this field of research on colds?

Mr. FOGARTY. Yes.

Dr. ANDREWS. Let me say first of all, there are more than 120 different types of so-called new viruses isolated and identified since 1948. Fifty of these already have been shown to cause respiratory diseases so there is a great assortment of causes which can result in

colds. About 20 of these agents are of great importance; they are the ones which cause the severe colds that you speak of, which seem to hang on. They are difficult to get rid of; they do make people very sick; and they are very contagious. And so we are constructing our vaccine, our first go at it, at least, using 4 of these 20 agents. These are respiratory syncytial viruses, parainfluenza viruses, adenoviruses, and the Eaton agent, which is a pleuropneumonia-like organism.

These are the four newer etiologic agents which cause much of the severe cases of upper respiratory disease.

We have six contracts, which have been given to commercial pharmaceutical firms, for the production of prototype vaccines against these agents.

These six contracts amount to about \$11½ million thus far, with additional contracts to be awarded.

In addition to the contracts for the development and production of the common cold vaccines, we have nine contracts for the clinical evaluation of these vaccines, because they must be tested on different types of population, age, and employment groups in different parts of the country; and so we have nine contracts for the clinical evaluation of these vaccines which runs about a third of a million dollars—\$335,000. Specifications for these contracts are continuously reviewed by a panel of consultants developed for this purpose.

PATENT RIGHTS TO VACCINE

Mr. FOGARTY. Do you have any problem with patents?

Dr. ANDREWS. We have not experienced them yet, but I expect this may be a possibility in the future. I know that some of the other institutes are having difficulties of this kind.

Mr. FOGARTY. Do you have the same arrangements as the cancer chemotherapy program?

Dr. ANDREWS. No. We use the standard clause employed by the Public Health Service to cover patents. The cancer chemotherapy program has a mechanism which enables it to negotiate on a different basis.

Mr. FOGARTY. All right. Suppose you make a contract with a pharmaceutical house. You have five or six or seven.

Dr. ANDREWS. Yes.

Mr. FOGARTY. And one of them comes up with a vaccine. What happens?

Dr. ANDREWS. This is public property by the terms of the contract.

SPECIAL REPORT ON RESPIRATORY DISEASE AND VACCINE DEVELOPMENT

Mr. FOGARTY. We will place your special report on respiratory disease and vaccine development in the record.

(The report follows:)

During the past year a conference on newer respiratory disease viruses provided a forum at which more than 400 virologists from this country and abroad were given the opportunity to assess, by means of reports, panel discussions and commentary by 60 experts, the current status of research on the viruses responsible for a large proportion of illnesses of the respiratory system. Sponsored by the University of Southern California, the conference was supported in part by a grant from the National Institute of Allergy and Infectious Diseases, whose scientists for the past decade have been leaders among investigators of viral diseases of the respiratory tract. The published proceedings of the conference

will provide a unique contemporary text on this subject. They will bring together in a single volume a view of present-day global progress against the wide-ranging viruses of respiratory disease, and present an informed assessment of the complexities of the unsolved problems with which the investigators in this field are contending.

An interesting paradox has become apparent in the 10-year period since recognition of the first adenoviruses, which were optimistically, though briefly, expected to be an answer to the problem of acute respiratory disease. Ten years ago, when the isolation of viruses was extremely complicated and difficult, scientists believed that once they could isolate and identify viruses at will the problem of acute respiratory disease would be solved with relative ease. Today the demonstration of viruses in relation to respiratory diseases has become a commonplace, but the intricacies of their roles in producing disease remain to be understood. Recent work discloses that in man and other living creatures viruses are incredibly numerous and prevalent. Fortunately, not all viruses cause disease. The multiplicity of viruses makes even more urgent the problem of identifying and coping with those which are implicated in human illness. The natural history and clinical importance of these viruses, some of which are now recognized in varying degrees, must be determined in continuing comprehensive clinical, laboratory, and epidemiological studies. The respiratory disease studies of the Institute encompass all these phases, both in intramural research programs and through the support of contract research and extramural research grants.

One intramural approach to the clinical study of respiratory viral agents has been the evaluation of experimental illnesses of the respiratory tract induced in volunteer patients. This year a new development is helping investigators to reproduce experimental illness comparable to natural infection. Previously, when virus had been given by coarse spray or nasopharyngeal instillation, it was difficult to estimate accurately not only the amount of virus retained but the actual site of inoculation. Now there is available an aerosol apparatus which permits the administration of a respiratory viral agent in an aerosol of submicron size. Quick and simple inoculation is performed in a completely equipped truck semitrailer designed and built by the staff of the biological laboratories at Fort Detrick. With this equipment investigators have been able to estimate rather precisely the smallest size of the viral dose required to produce infection, illness, and antibody response. Given specific information about particle size of the infective viral dosages and site of inoculation, our investigators have compared the disease produced by inoculation of virus into the lower pulmonary tract with that produced in the upper tract. Studies are also in prospect to determine the mechanism of natural airborne spread of respiratory viral disease. An important potential use of this equipment is its modification to provide rapid and accurate inhalation of viral vaccines.

One of the Institute's most valuable resources for the study of respiratory viral illnesses in babies and small children has been the long-term research program at Junior Village. Last year a published review of the first 3 years of the study provided some interesting epidemiological information. Among the accomplishments were the isolation of nearly 60 immunologically different viruses, many of which were previously unrecognized or unclassified. At least 10 virus serotypes are believed to be probable etiologic agents of some of the illnesses observed. Among the new viruses discussed in the report were four previously unrecognized adenoviruses, ECHO viruses, myxoviruses, parainfluenza viruses. The study also revealed a number of bacterial agents associated with the respiratory illnesses of the Junior Village Children. On the average each child at Junior Village has one new febrile illness every 3 weeks and a new bacterial or viral infection every 2 to 4 weeks.

The Junior Village studies continue to be a most fruitful source of new information about viruses. Detailed descriptions of the occurrence of adenoviruses types 1, 2, and 3 were completed in the past year, providing perhaps the best and most conclusive evidence on the role of these agents in human disease.

This population also provides an excellent milieu for the assessment of viral vaccines. The protective effect of poliovirus vaccine and of experimental measles vaccines (both killed and attenuated) has been measured. Even more important than the intrinsic worth of the data so accumulated is its value in establishing patterns for future evaluation of vaccines against respiratory disease.

The discovery last year that Eaton agent pneumonia was not a viral pneumonia has added another facet to the problem of respiratory disease. For many years thought to be a virus, Eaton agent is now known to be a pleuropneumonia-

like organism (PPLO), bringing still another microbial group forward as a factor in undifferentiated respiratory illnesses. This discovery by an Institute scientist and his colleagues was the second in medical history to associate PPLO with human illness, although PPLO has been known to be important as a cause of disease in poultry and livestock. In the past year our scientists have been devising workable means to isolate PPLO from infected patients. They have developed methods for recovery of Eaton agent on artificial medium, and they can now grow the organism in broth. With this latter accomplishment, it is possible to prepare a specific complement-fixing antigen. The problem of identifying PPLO in the blood is thus considerably simplified.

To explore further the relationship of PPLO to human disease, scientists must devise improved means of cultivating and identifying these elusive organisms. Studies are already underway in the Institute to learn more about the biological and antigenic interrelationships of PPLO, with a view to relating this basic information to the problem of PPLO as a cause of pneumonia and possibly other undifferentiated respiratory illnesses.

Perhaps the most valuable advance in the search for understanding and conquest of respiratory disease will come with recognition by health authorities and the public itself that this vast body of illness is indeed a public health problem. It is paradoxical that this is not already clearly recognized since current surveys and population samplings indicate that acute respiratory illness is responsible for more morbidity than all other illnesses combined. Continuous contemporary estimates of respiratory disease prevalence do not now exist, yet significant control of acute respiratory diseases will be more readily achieved only when there are available accurate nationwide prevalence data which will better define the extent of the problem.

Early last year Surgeon General Luther L. Terry announced the inauguration within the Public Health Service of a vaccine development program designed to speed the day when safe and potent vaccines against viral respiratory diseases will be available to the public. The program, under the direction of the National Institute of Allergy and Infectious Diseases advised by a board for vaccine development, is laying the foundation to help achieve the long-range goal set forth by Surgeon General Terry.

The six-member board for vaccine development is composed of four university scientists with strong interests and competencies in respiratory disease research and two Institute scientists whose laboratory findings of the past few years have done much to give impetus to the broad concept of control by vaccine prophylaxis of viral diseases of the respiratory tract.

The initial efforts of the vaccine development program are concentrated on developing experimental vaccines against those viruses now known to cause a major portion of acute respiratory illness in children and in closely confined groups such as military populations, college students, and prisoners. Prototype vaccines are being attempted first against respiratory syncytial virus; parainfluenza viruses 1, 2, and 3; Eaton agent; and some of the adenoviruses.

Two categories of contracts have been designed. One is for the actual production by commercial pharmaceutical research groups of prototype viral vaccines. The other type is for clinical testing to evaluate the safety and potency of experimental vaccines as they become available. Initial efforts will be confined to devising viral antigens which can be used singly or in combination to protect those special groups in the population in which respiratory disease has been most clearly defined.

In the first year of the program, 10 contracts have been awarded to 9 institutions, for a total of \$1.2 million. The commercial firms that have received contracts are Abbott Laboratories, Cutter Laboratories, the National Drug Co., Charles Pfizer & Co., Inc., and Wyeth Laboratories. The clinical evaluation centers are Children's Hospital of the District of Columbia, the University of Colorado Medical Center, Hektoen Institute for Medical Research of the Cook County Hospital, and Tulane University.

Scientists working in this field recognize that it may be numbers of years before all long-range goals can be achieved in controlling in this country alone the massive problem of viral respiratory disease. Investigators committed to this approach are aware that they may have to deal in this research area with graver complexities than those previously encountered in programs of immunization against other viral diseases. They understand that the unprecedented multiplicity of viruses involved, the relatively short span of infectivity of these viruses, and the difficulty in achieving and maintaining effective levels of

immunity, are complicating factors of presently unknown magnitude. Enormous effort and resources will undoubtedly be required to modify significantly the present pattern of respiratory disease. The investigators working toward this goal are cautiously optimistic that the scientific information available to them today is a firm and reasonable basis from which to make a start.

The vaccine development program marks a beginning in a nationwide attempt to put to the best use existing knowledge of the viruses that cause serious respiratory illnesses. Information which develops as a result of the program is expected to broaden still further the base from which to consider new and improved approaches to the control and amelioration of these illnesses.

ASTHMA RESEARCH

Mr. FOGARTY. What about asthma? Are you working on this problem?

Dr. ANDREWS. Not intensively, but it is related to some of the work which we do.

This is usually a sensitization of lung tissue, a sensitivity to any one of a great variety of external agents, and sometimes, to internal ones—to diseases which are already in progress and which have created some tissue sensitivity. A person then has episodes of asthma and it can be very dangerous.

Mr. FOGARTY. Those with asthma are more likely to have complications if they get one of these respiratory infections. It could lead to pneumonia.

Dr. ANDREWS. Yes. Occasionally, it does.

GRANTS PROGRAM LEVEL

Mr. FOGARTY. Most of your increase is in research grants, \$2,981,000 but we run into that standard leveling off pattern. Your budget is geared to financing 355 new grants in 1964 compared with 355 in 1963. Is that right?

Dr. ANDREWS. Yes, sir. I believe so.

Mr. FOGARTY. Do you think you will have any approved applications that you will not be able to finance this year?

Dr. ANDREWS. 1963?

Mr. FOGARTY. Yes.

Dr. ANDREWS. There is a deficit of \$3,127,000 worth of grants, this year.

Mr. FOGARTY. Do you expect an increase in approvable grants next year?

Dr. ANDREWS. I think this is possible, but I do not know that there is any assurance of it, at the present time.

COOPERATION WITH WHO AND PAHO

Mr. FOGARTY. Can you tell us a little bit more than you did in your statement, about your work in tropical medicine through the WHO and the Pan American Health Organization?

Dr. ANDREWS. As part of its research program in tropical medicine and parasitology, the National Institute of Allergy and Infectious Diseases provides grant support to two international bodies engaged in medical research, the World Health Organization (WHO) and the Pan American Health Organization (PAHO). Currently, NIAID grants to WHO total \$276,000; \$188,000 for research on virus

diseases, immunological surveys, and vaccine studies, and \$88,000 for studies of bilharziasis (schistosomiasis).

Under an agreement between PAHO and the Public Health Service, this Institute has two active grants in support of projects conducted by PAHO. The first grant, amounting to \$33,607, was made to the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City for a study on the interrelation of viruses, diarrhea, and nutrition. The second grant, for \$4,600, was awarded to the Pan American Sanitary Bureau (PASB) for a study on methods of treating canine echinococcosis, a tapeworm disease of dogs which resembles similar infections in humans. (INCAP is one of three PAHO centers for research and training. PASB is the secretariat and operating arm of PAHO.)

In addition to its grants to WHO and PAHO, NIAID has made research grants of \$143,879 to the Gorgas Memorial Laboratory in the Republic of Panama in addition to the \$250,000 appropriated specifically for this laboratory. These grants are distributed as follows: \$66,516 for research on the transmission of leishmaniasis, an infection caused by protozoan parasites; \$54,370 for an investigation of the ecology of arthropod-borne viruses; and \$22,993 for a study of the ecology of sylvan yellow fever.

The relationship between the intramural programs of NIAID and the two international health organizations is essentially a two-way street. From time to time, NIAID scientists are detailed to WHO on special assignment. Other investigators from this Institute work under the sponsorship of PAHO in many countries of Latin America. Whenever the Institute wishes to follow a line of scientific inquiry in a PAHO member country, PASB acts as go-between and assists in arranging the details of the project. PASB also participates in the transportation of scientific materials between the host nation and the NIAID laboratories. In turn, scientists at the Institute's Middle America Research Unit (MARU) in the Panama Canal Zone provide consultation and special laboratory diagnostic services to PAHO member nations when called upon. In sum, NIAID's relations with WHO and PAHO are cooperative, productive, mutually beneficial, and scientifically profitable.

HEMORRHAGIC FEVER IN BOLIVIA

Most of the work which we have done through these organizations has been carried on by the Middle America Research Unit, which is located in Panama. During this year, the Pan American Health Organization requested that the Middle America Research Unit give assistance to the country of Bolivia, and this request was seconded by the Bolivian Department of Public Health.

They have been experiencing, over a number of years, a disease about which little has been known. It manifests itself slowly, but ultimately, people develop great bleeding propensities. They bleed from all the exits of the body and the death rate amongst these people with this "hemorrhagic fever," as it has come to be called, is roughly 33 $\frac{1}{3}$ percent, a terrifically high ratio of deaths to cases.

Mr. FOGARTY. Is it anything like leukemia?

EXTENT OF DISEASE

Dr. ANDREWS. No. Not at all. As far as we can make out, it is an entirely different kind of disease. The people get panicky; they leave their homes; sometimes they burn their houses. The area of Bolivia in which this disease occurs is up in the northeastern section, originally designed for colonization by the Bolivian Government. So it is very disappointing for them to find out that people are leaving there, and going to places where this disease has not yet existed.

Our scientists at the Middle America Research Unit have studied this very carefully, both from the epidemiologic standpoint, and from the standpoint of the laboratory operations. They have come to the conclusion that this is probably a viral disease, and is very similar to a disease in Argentina caused by a virus known as the El Junin virus because it was very active in one of the cities by that name in northern Argentina.

Some of my friends in Brazil tell me that there have been mysterious cases of hemorrhagic-feverlike disease on the Brazilian side; so that we suppose this may be a disease of considerable dimensions in South America. The Middle America Research Unit is back working on this disease in Bolivia, with the objective of establishing the identity of the disease, whether or not it has animal vectors which are carrying it from what reservoir animals, and the actual distribution of the disease throughout South America.

This must be a horrifying experience for these people; even those who recover are marked definitely for a long time. The girls, especially, lose much of their hair, that is, they develop alopecia, if they recover from this disease.

Mr. FOGARTY. You say your people in the Middle America group are doing some of this research?

Dr. ANDREWS. Yes. They are carrying on this research. They are now in their second year.

Mr. FOGARTY. How do you get along with the health people in Bolivia?

Dr. ANDREWS. Oh, there have been nothing but the most cordial relations, to my knowledge.

Mr. FOGARTY. In some other areas, like foreign aid, there have been complaints, you know, about Bolivia. I just wanted to know how you were getting along with the medical people.

Dr. ANDREWS. I think they have welcomed the opportunity to utilize the facilities and experience of our people from the Middle America Research Unit in the Panama Canal Zone.

Mr. FOGARTY. What were you going to say, Dr. Shannon?

SIGNIFICANCE OF RESEARCH TO PAN-AMERICAN PROGRAMS

Dr. SHANNON. I was going to say—this is important. It is even much more broadly significant than brought out by Dr. Andrews.

The best one can guess at the present time—at least, one can be certain that the potential area of the disease is the entire so-called Pampas Belt that lies to the east of the Andes Mountains. This is a very fertile area, where people could move into. The situation at the present, with the epidemic disease that has a mortality rate as high as 30 percent, is that these lands are practically useless, due to

the infection. So we look on this as a tremendous opportunity, indirectly, to provide a very broad benefit for our pan-American program; simply from doing our own job well. One hopes here, of course, to find the bacteria or the insect or the animal and then, at a later time, to develop vaccines opposing the disease, which would basically result in the opening up of very wide territory. So this has a very profound economic consequence.

ROCKY MOUNTAIN SPOTTED FEVER

MR. FOGARTY. Would someone just very briefly tell us the history of the Rocky Mountain spotted fever problem? What you did about it and the final results. I think that is a real good example of the worthwhile, money-saving results of research done by the Public Health Service.

What was the problem, originally?

DR. ANDREWS. Yes. Years ago, some areas in the northwestern part of the country were rendered almost uninhabitable, by the presence of a disease about which little was known. In fact, nothing was known. Then, the State of Montana built a laboratory, now the Rocky Mountain Laboratory in Hamilton, Mont., for the express purpose of doing research in this area on this particular disease, known as Rocky Mountain spotted fever.

A number of scientists died in the process of working on this disease.

MR. FOGARTY. Put what they did and their names in the record.

DR. ANDREWS. Yes, sir. There is an excellent account of this whole development available. We will enter it in the record.

(The material follows:)

ROCKY MOUNTAIN SPOTTED FEVER

The story of the conquest of spotted fever represents an important contribution by the Rocky Mountain Laboratory to public health progress and also illustrates how a seemingly provincial public health approach may turn out to be lifesaving for the Nation.

The first studies of spotted fever were begun in 1902, by Drs. L. B. Wilson and W. M. Chowning of the University of Minnesota, at the request of Dr. A. F. Longeway, secretary of the then newly created Montana State Board of Health. At that time spotted fever was known in other parts of the Rocky Mountain region, but in none of them was it as severe as in the Bitterroot Valley, where more than 80 percent of adults who contracted the disease died.

For several years following this initial research, other investigators studied the disease. One of them, Dr. Howard Taylor Ricketts, of the University of Chicago, carried on work in the Bitterroot Valley each spring from 1906 to 1908, and it was he who proved that the Rocky Mountain wood tick, *Dermacentor andersoni*, was the agent responsible for transmitting this disease to men.

Eventually it became apparent, however, that tick-control measures alone would never solve the spotted fever problem. The State Health Department and the U.S. Public Health Service brought their combined resources to bear upon this disease. Finally, an experimental vaccine was developed and proven effective through trials in large numbers of guinea pigs. In spite of all safety precautions that could be devised at the time, a total of five research scientists and laboratory workers who had become exposed to the highly infectious rickettsial organism contracted Rocky Mountain spotted fever and died. These were: Dr. Thomas B. McClintic, USPHS, 1912; Dr. Arthur H. McGray, Montana State bacteriologist, 1919; William Edwin Gittinger, USPHS, 1922; George Henry Cowan, Montana State Board of Entomology fieldworker, 1922; Arthur LeRoy Kerlee, USPHS, 1928.

Mr. FOGARTY. What is the disease like?

Dr. ANDREWS. It is a typhuslike disease, transmitted by the local ticks in this area.

Mr. FOGARTY. Does it go as far west as Washington?

Dr. ANDREWS. No, sir. It is in the Bitterroot Valley, primarily.

Dr. SHANNON. Mr. Fogarty, this is a very complex story. We can supply it for the record. I can point out the highlights.

This was a new disease, newly described, and had a high mortality rate. The center of the focus was in the Bitterroot Valley in Montana, and it was early in the century that Montana became quite concerned, and they set up a laboratory. They found themselves quite incapable of solving the problem so they sought help from the Public Health Service.

The Public Health Service put out a fairly large number of people for that time, to resolve the problem.

The first thing they did was to describe the extensiveness of the disease from the points of high concentration.

The second thing they found was that the disease was due to rickettsia.

The third thing they found was the specific tick that transmitted the disease.

The fourth thing was to develop the vaccine that would prevent the disease.

This vaccine, I might say, is now used throughout the United States, and you may recall when your children go to camp in the summer, in certain areas of the country, they may be advised to take this vaccine against Rocky Mountain fever.

TYPHUS VACCINE

They experienced something even more important in this work on Rocky Mountain spotted fever than just opening up an area of the United States for general use, because the scientists who were involved in studying this disease then moved over into a much more widely spread disease of world importance; namely, typhus. The basic techniques for defining the disease and developing vaccine against the Rocky Mountain fever was the basis of our total immunization program for typhus during World War II. The interesting thing there is, the last time I checked the results, this vaccine produced such a solid immunization for typhus that not a single American soldier came down with the disease.

Mr. FOGARTY. I was going to ask about that earlier in the hearings. Someone was complaining about the fact that there was too much money being spent. I thought the Public Health Service was responsible for developing this vaccine that prevented this disease in the soldiers overseas.

Dr. SHANNON. Yes, sir. I think this whole story might well be spread on the record. We would be glad to do it sir.

Mr. FOGARTY. All right.

(The information follows:)

TYPHUS VACCINE

The success of the Rocky Mountain Laboratory against spotted fever and the background of scientific information acquired during this work provided a beach-head for mounting an attack on a number of other disease problems, including tick- and mosquito-borne infections for which animals are the reservoirs. Noteworthy in this respect was the extension and application by another group of scientists of the new technique of growing the spotted fever rickettsia in embryonated chicken eggs to the culture of the rickettsia causing typhus fever. This led directly to the successful development for the first time of a vaccine of incalculable value to the Allied forces during World War II against this widespread and extremely deadly disease.

ROCKY MOUNTAIN LABORATORY ACTIVITIES

Dr. ANDREWS. I think you might be interested in hearing a little something about the proposed activities at the Rocky Mountain Laboratory.

Mr. FOGARTY. Yes. Go ahead.

Dr. ANDREWS. You are aware, I am sure, that most of the viral agents which have been mentioned here, cause sharp, acute, self-limited types of disease, but there are types of viruses which cause prolonged and indolent diseases. The remoteness of the Rocky Mountain Laboratory, plus the fact that during this last year it has been possible to add better facilities for handling "hot" agents out there, plus the third fact that we have recovered an excellent veterinary pathologist, who was there previously, now make it possible to study some of these viruses with prolonged incubation periods, and extended periods of activity.

SCRAPIE RESEARCH

One of these is known as scrapie; this is an English name. The disease occurs in sheep and goats. It is a neurologic disease. Ultimately, the afflicted animals itch a great deal and scrape themselves against stone walls and bars and enclosures of this sort, scraping off their wool and skin, and this is how the name "scrapie" got to be applied to the disease.

They already have this virus at the laboratory.

Mr. FOGARTY. Is this very widespread among the sheep?

Dr. ANDREWS. Yes; it was introduced from Europe, I think, by way of England, into Canada, and from Canada it was spread down to the United States.

So that this is a disease of some concern to the Department of Agriculture. In fact, we had considerable difficulty in getting the virus of this disease to use experimentally. However, we are interested because these chronic viral infections of animals may represent models of similar, protracted viral diseases of man.

ALEUTIAN MINK DISEASE

The second disease which the Rocky Mountain Laboratory wishes to work upon is called the Aleutian mink disease and this is a degenerative disorder of connective tissue, and can be bracketed with the autoallergic diseases, about which I would like to say something in a

short time. This can be studied. This is somewhat like lupus erythematosus, and has been studied only with weaned mink, thus far, and this is why it gets its name. These are the only animals which can be used to work with, experimentally. Again, we believe we have a prototype of human disease of a degenerative nature.

Mr. FOGARTY. What is lupus?

Dr. ANDREWS. Lupus belongs to a group of diseases in which afflicted persons are susceptible to their own antibodies and develop sensitivity against certain of their own tissues. In lupus, it is largely skin and subcutaneous tissues which are attacked and degenerate.

I was going to say something about this general area of diseases because this is a matter of great interest to us, and because of the immunity factors concerned in it.

In fact, I can go directly to that.

ANTIMETABOLITE DRUGS FOR TREATMENT OF AUTOALLERGIES

We have, in our own clinical facility at NIH, been able to get a few cases of nephrosis. This is a kidney disease—a degenerative kidney disease, perhaps one of autoallergy diseases which involve such tissues as kidney tissue, nervous tissue, liver tissue, and skin and connective tissue.

Mr. FOGARTY. What do you mean by autoallergy?

Dr. ANDREWS. I mean by this that the individuals who have these diseases have antibodies formed within their own bodies against certain of their own tissues, and this results, ultimately, in the destruction of some of these tissues by these antibodies.

Now, in this type of disease, the big development which has occurred this year in our laboratories is the use of antimetabolite drugs which prevent the activity of the cells of the body which develop the serum globulin in which antibodies are contained, and are distributed through the body.

Thus, for the first time, it has been possible to produce remissions in a disease which has been considered utterly intractable in the past, because people who have had lupus erythematosus or these other types of autosensitizing diseases have had virtually no expectation of a cure. We regard this as a very brilliant advance in the handling of this disease.

ANTIMETABOLITE DRUGS AID IN KIDNEY TRANSPLANTS

Now, then, the immunologic principle applies also in another field, where we have been supporting, together with some of the other institutes, work at Harvard in the transplantation of organs from one individual animal to another. The grantees have completed something like 300 successful transfers of kidneys in dogs.

I am not sure you realize that ordinarily, when you take tissue from one individual and transplant it to another, that it is only a short time before this graft is rejected. The host body produces antibodies against this foreign tissue, and the tissue cannot be retained.

To a certain degree, this can be overcome by radiation and also by the use of antimetabolite drugs. This has now progressed to the stage where the surgeons who were interested in the dog kidney trans-

plantations now have two young men in Boston walking around with kidneys, including one each, that they did not come by naturally.

This new kidney was implanted in them surgically, one from a hydrocephalic child, as I recall, immediately after it expired; the other came from the victim of an automobile accident. This was over 6 months ago. By using the same surgical techniques which had been developed for the dogs, surgeons gave these young men apparently healthy pairs of kidneys to live with for the rest of their lives.

I presume they may have to continue to take this drug which, in effect, prevents the formation of antibodies against this newly introduced kidney tissue.

Now, we have two more similar instances, again in our grantees. These are in Colorado; but the operation and the treatment are the very same. In this instance, a mother offered a kidney for her son: one of her kidneys was removed surgically and transplanted in her son, using the antimetabolite drugs; and another instance in Colorado was where a wife gave one of her kidneys to her husband.

Mr. FOGARTY. The operation used to be performed just on twins.

Dr. ANDREWS. In the case of identical twins, this can be done because the tissue which is transplanted from one such individual to the other is not susceptible to the antibody reactions.

Mr. FOGARTY. What happens to the person who gives the kidney?

Dr. ANDREWS. Oh, you can get along on one kidney very easily. The remaining kidney increases in size somewhat and thus compensates to a certain degree by taking over the function of both kidneys: but you are out of luck if you lose the second one! That is the great hazard of having only one kidney.

Mr. FOGARTY. Is there anything else you want to say?

GORGAS MEMORIAL LABORATORY

Dr. ANDREWS. May I speak about the Gorgas Memorial Laboratory for a moment?

Mr. FOGARTY. Surely.

Dr. ANDREWS. You will recall that funds were made available to Gorgas for a new laboratory building. Only a few weeks ago, Dr. Shannon and I had the opportunity of visiting this establishment and seeing the new laboratory which is large and spacious, and at that time, was not occupied. I suppose by now, some of it is.

This will provide Gorgas with an opportunity to do more sophisticated laboratory research than they have in the past; and to employ more laboratory scientists.

There is still very much concern with the epidemiology of disease in Panama and in the general area of the isthmus. The Gorgas Memorial Laboratory has made an application to our Institute for support for a very extended piece of research in the lowest part of Panama; the part which is closest to Colombia.

This is the area in which the last segment of the Trans-Isthmian Highway will be built, and it is presumed that in the survey and construction necessary for this operation, there could be a considerable amount of sickness, as there was in the building of the canal; but this of course, remains to be seen.

The Gorgas Laboratory has been given the opportunity by the Health Department of Panama to carry on special research to see what can be learned from this experience.

RESEARCH CAREER AWARDS

Mr. FOGARTY. From the justifications on page 54, you think rather highly of the research career award program and say it "is in its second year of accelerated growth." Then the table on the next page shows the 1964 increase—zero. What happened, between the pages?

Mr. KELLY. I think the accelerated growth referred to the period up to 1963—not to the budget year.

Mr. FOGARTY. So that is leveling off, too, even though you think rather highly of this research career award program. Isn't it working out pretty well?

Dr. SHANNON. In the overall fellowship program, this Institute is supporting 254 fellows, of which 84 are research awards. This includes both the younger departmental awards, as well as the career awards themselves.

In addition, they are supporting 57 special fellowships. These are for special purposes, to satisfy generally, short-term experiences or special training opportunities.

Mr. FOGARTY. What are you leveling it off for?

Dr. SHANNON. Well, on balance, in the face of funds that were available for Dr. Andrews to distribute, we felt a shortage of funds in the research grants area; and we would rather hold this program at the present level, than reduce the grants.

TRAINING GRANTS

Mr. FOGARTY. There certainly is not a big increase under fellowships and training, is there?

I thought this was an area in which you really needed help.

Dr. ANDREWS. Yes. We are aware of this and we hope that by 1970 that we will have double the scientific personnel presently concerned in this activity.

Mr. FOGARTY. How are you ever going to get it doubled with this kind of a budget?

It is less than a 10-percent increase. Is this your recommendation?

Dr. ANDREWS. Well, what I would like to see in Congress next year would be a 15-percent increase, which should take us up to about 100 percent by the time we get to 1970 and this would have the effect of doubling our personnel involved there.

Mr. FOGARTY. What did they do? Catch you in a squeeze here?

Dr. ANDREWS. Well, I don't really know how to explain it.

Mr. FOGARTY. It looks to me as though everybody in the Public Health Service is being held down except Mental Health, and I think their budget is conservative.

VACCINE EVALUATION CENTERS

What are the vaccine evaluation centers mentioned on page 70?

Dr. ANDREWS. These are schools, very largely. The universities which have accepted contracts to test these vaccines in special populations.

Mr. FOGARTY. I thought the Biologics Standards was doing about the same thing.

Dr. ANDREWS. They have not been concerned thus far in the common cold vaccine under our program of development. Ultimately, this will get to be part of their concern.

Dr. SHANNON. I would like to comment on this, because this is very pertinent to one of the basic issues of our program.

We feel that at this stage of the Institute's involvement in vaccine development, they can do it on a straightforward, scientific basis. If we were to change from university to industry—go where one will, for help—at this particular stage, it would be unwise to control the scientific development of a program leading to a product. So you will find in general, the Division of Biologics Standards will not step into the picture until a definitive vaccine has been conceived, at which time they become very much interested. But at this stage, it is primarily the responsibility of this Institute.

STATEMENTS ON RESEARCH PROGRAMS

Mr. FOGARTY. Doctor, will supply for the record a statement about what you are doing in the area of hay fever?

Dr. ANDREWS. Yes, sir.

Mr. FOGARTY. A statement on eczema; a statement on bacterial diseases; one on encephalitis; a statement on germ-free animal research; one on virus-free animals; one on nephrosis; and one on the Rocky Mountain Laboratory.

(The statements follow:)

HAY FEVER AND ASTHMA

More than 10 million of our people suffer from hay fever and asthma. Much of the Institute's allergy research is directed against these prevalent forms of hypersensitivity. More than a half million dollars has been invested, for example, in grants to 29 universities for research on airborne allergens, particularly on the pollen of the giant ragweed, most common cause of pollen hay fever in this country.

This pollen, and other allergens, are the concern of the Institute's allergen standardization program, established to provide reliable and comparable allergen derivatives and to aid communications between investigators working in similar fields of allergy. In 1964, the allergen standardization program will be transferred to the collaborative (contracts) areas, where information gained thus far will be put to use through the contract mechanism. The objectives are the large-scale production of standardized ragweed pollen fractions essential for research and the distribution of the antigen to various investigators, including many of the Institute's grantees.

In the Institute's Laboratory of Immunology, the skin-sensitizing agent in ragweed-sensitive individuals has been identified—a clue to the essential protein or proteins causing hay fever and a finding promising for an investigation of antibody activities associated with this material.

The Clinical Research Center program of the National Institute of Allergy and Infectious Diseases is preparing to give a high priority to clinical studies of hay fever and asthma. These centers employ grant funds to provide for extensive and unified interdepartmental clinical research and training. For example,

at the University of Colorado Medical Center a project under the Clinical Research Center program is concerned with physiologic responses of asthmatic patients. Concurrent administration of adrenalin and histamine is being observed, employing electronic recorders to chart patient responses.

Other investigators under the research grants program (115 grants amounting to about \$3 million are devoted to studies of allergy) have helped to define the limitations of air-filtering devices in removing allergens from room environments; have set up immunological, meteorological, botanical, and biochemical studies related to ragweed hay fever; and have examined the use of "one-shot" desensitizing injections in place of many injections. The injection of a single emulsified desensitizing substance is a method endorsed by some clinical allergists but not by all. When this emulsion is injected, much higher concentrations of extracts can be maintained because the mixture is absorbed only gradually by the tissues. However, some allergists have reported more adverse reactions with the emulsified antigen than with conventional materials. This is a consideration of which the importance must be clearly evaluated through further clinical research.

In the absence of clear and complete understanding of the mechanisms of allergy, much information is being gained through empirical methods. One grant-supported study by the University of Michigan School of Public Health, is based on responses from 6,995 of about 9,800 inhabitants of the town of Tecumseh, where information about hay fever and asthma cases is being collected throughout a total community. Preliminary results indicate that, although frequently there is correlation between hay fever and asthma, this relationship is not one in which hay fever inevitably leads to asthma. The latter condition, incidentally, is one that can be more serious than is generally realized. Prolonged difficulty in breathing often leads to crippling lung damage—one reason that allergists recommend early attention for hay fever or asthma.

While research by the National Institute of Allergy and Infectious Diseases and its grantees is leading to improved amelioration of symptoms and a better understanding of the clinical nature of asthma and hay fever, the greatest hope still lies in basic research. This is the major emphasis of the NIAID's Laboratory of Immunology and the program of research grants. In the latter, 61 grants in the amount of \$1,738,000 are assigned to fundamental studies of allergy. An understanding of the immune mechanisms of the body—which react helpfully in defense against disease, harmfully in certain persons in the abnormal response of allergy—should lead the way to cure and perhaps to prevention of hay fever, asthma, and a host of other allergic diseases. They are different manifestations of the same abnormal immune response—the complex reaction we call by the simple term "allergy."

ECZEMA

Despite the great volume of current research in modern dermatology, the eczemas which plague so many of our people remain among the most baffling of diseases. Sometimes a single manifestation may reflect a combination of disturbances: microbiologic, metabolic, and emotional. The complete solution of such a problem requires of life processes a more fundamental understanding than we yet possess. The National Institute of Allergy and Infectious Diseases is studying certain skin diseases from the standpoint of allergy-immunology and microbiology. Others of the National Institutes of Health also contribute to continuing research on skin disorders.

The National Institute of Arthritis and Metabolic Diseases, for example, supports many studies concerned with metabolism within the skin and how this mechanism is influenced by the use of drugs. Similarly, it conducts numerous morphologic studies of skin. A report to the House committee on this work by NIAMD was published on page 1395 of the hearings for fiscal year 1963.

Prevalent eczemas of allergic origin, as well as skin disorders resulting from infections by viruses, fungi, bacteria, or other micro-organisms, are being explored by the National Institute of Allergy and Infectious Diseases. An Institute grantee at Dartmouth has reported on the double jeopardy caused not merely by invasion of the epidermis by pathogenic fungi but also by the allergic response of the skin to biochemical constituents of the fungi.

The problem of eczema caused by allergy may begin early in life. In some cases of the childhood type of eczema, the rash is very mild; in other cases it is severe and spreads over the entire body. Scratching by the child may produce infection, which can become serious. In most cases an infant out-

grows eczema, but it may return after the child is older. Eczema in the child is usually a result of allergy. In infants and young children, foods are the most common cause. Inhaled substances can also cause eczema. Typical allergens are ragweed, pollen, eggs, milk, fish, feathers, and wheat. Hives and giant swelling may also come from allergies to such substances as strawberries, penicillin, peaches, melon, and aspirin. These reactions appear only in persons who are allergic, that is, hypersensitive, to the particular material and do not occur in "normal" individuals.

Eliminating the cause of the reaction, if that is possible, is the best preventive measure. Desensitization by administering extremely small amounts of the offending material under careful medical supervision is another measure. Many research projects conducted by the National Institute of Allergy and Infectious Diseases seek the most effective means of desensitization, the identification of the precise proteins involved in sensitivity reactions, the purification of materials, and the standardization of allergenic extracts to make them reliable and widely available. Lotions and ointments recommended by a physician may bring partial relief to the sufferer from eczema. In severe cases, drugs can be prescribed.

Institute grantees at the University of Cincinnati College of Medicine recently described tests which may quickly identify infants ill with milk allergy when a variety of symptoms are involved.

The typical rashes of teenagers usually represent more complex problems of metabolism, unless hypersensitivity or infection is present. In the absence of truly preventive or curative measures being sought by medical science, adequate rest, good diet, and cleanliness remain the basic prescription in many cases.

Skin reactions of allergic nature may be traced to material in the home environment, perhaps to cleaning compounds, or even to that disreputable conglomerate called "house dust." The nature of the sensitizing materials in house dust is being studied by the Institute's Laboratory of Immunology. These are materials normally harmless to most individuals; allergy is hypersensitivity. Some 17 million of our people suffer from one or another form of allergy.

The industrial skin diseases constitute a major area of research. It has been estimated that 1 percent of the industrial workers in the United States, not including clerical employees, are affected annually with occupational dermatoses (**one in five of which are allergic in nature**) at a loss of more than \$100 million each year. Grant-supported studies of the mechanism of allergic eczematous contact dermatitis conducted by New York University have helped clarify some of the mechanisms of contact dermatitis by employing radioactive mercury salts; and at the University of Pennsylvania School of Medicine Institute grantees recently described means they developed for washing skin and cleaning the working environment with an antichrome solution designed to protect against chromium dermatitis—a frequent problem, for example, in lithographing and printing plants.

The infectious agents that cause skin reactions may be simple or difficult to counteract. The herpes viruses that cause various types of skin lesions, including "shingles," are, like most viruses, little understood; but few fields of research are more strongly supported than virology. A striking example of the relevance of research on the molecular biology of viruses to the control of human viral disease has recently been provided by the demonstrations of Kaufman and coworkers at the University of Florida that the nucleoside analog, bromodeoxyuridine, is an effective agent in the treatment of herpes keratitis. Some of the fundamental work defining effects of this and related compounds on the multiplication of viruses is being carried out by the Institute's Laboratory of the Biology of Viruses.

New knowledge resulting from basic research in virology almost invariably leads eventually to advances in medical practice, even though at times this occurs by somewhat devious routes. The relationship of the lesions of herpes zoster to the pox of chickenpox is still being studied by many investigators. Institute grantees at Harvard, for example, have helped to define this relationship through demonstration in tissue culture that cross-reactions occur between particles from the blood of patients with shingles and those with chickenpox.

Actually, the problem of skin diseases crosses categorical boundaries and concerns the research in neurology and metabolism as well as the scientist in allergy and infectious disease research. Manifestations range from simple eczemas to virus-caused warts—even, perhaps, to cancer of the skin. Basic findings from medical research undoubtedly will delineate the causes of skin disorders and will lead to methods of diagnosis, cure, or outright prevention.

Many research organizations are concerned with this area of research because it offers at one and the same time the opportunity for advances in basic and in applied research. For example, the Public Health Service's Division of Occupational Health has a strong interest in the broad range of industrial dermatoses.

BACTERIAL DISEASES

The bulk of recognized infectious diseases which plague men are caused by the one-celled microbes classified as bacteria. Occasionally one form or another emerges as a special problem; for example, resistant forms of staphylococci have challenged medical science in recent years. The advent of new forms of antibiotics to counter the resistant forms of this micro-organism has lessened the problem, but staphylococcal infections remain prevalent and troublesome. The National Institute of Allergy and Infectious Diseases supports a total of 79 grants in the amount of more than \$1½ million directed against this pathogen, alone. Many of these grants represent clinical studies in the Nation's leading hospitals, where the most efficient means of antiseptics against staphylococcal infection are being demonstrated, and information about these methods is being made available to other clinical facilities.

At present, several kinds of bacterial diseases constitute continuing cause for concern in the United States. These are respiratory tract infections by drug resistant strains of streptococcus; diphtheria and hemophilus organisms; urinary tract infections that are especially troublesome in women during their childbearing years, in girls and in the aged; infant diarrhea; staphylococcal and pseudomonas infections which have become difficult hospital management problems; and refractory tuberculosis resistant to streptomycin and isoniazid therapy.

Taken as a whole these diseases and a large number of lesser ones represent a continuing menace of sizable proportions. Research is being supported across a broad front to enhance natural resistance factors, develop new antibiotics and determine promising new avenues of attack on these persistent infectious bacterial problems.

At Bethesda, in the Laboratory of Bacterial Diseases, the National Institute of Allergy and Infectious Diseases is devoting a major research effort to basic studies of intracellular parasitism. These investigations of host-parasite relationships hold much promise of increasing our understanding of disease and immunity in relation to myriad bacterial infections. Specific research underway deals with possible changes in characteristics of infected, normal and immune cells, and the effect of the intracellular environment on the infecting organism. One aspect of this research is the investigation of antibody production by cells in the test tube.

Studies of human and animal brucellosis have been a long-term interest of the Laboratory. Effective medical treatment is now available for human cases, and a successful control program is reducing the incidence of bovine brucellosis in the United States. The Laboratory is collaborating with the World Health Organization and with other brucellosis research centers throughout the world on many problems, including clarification of the epidemiology of the disease.

Other research in this Laboratory deals with *Pseudomonas*, which is emerging as an organism of considerable importance in debilitated, burned, and chronically ill patients, and with L forms of bacteria which are still little understood.

The Institute's Laboratory of Infectious Diseases, in collaboration with the Wistar Institute of Philadelphia, has demonstrated that an important pneumonia-causing organism, the Eaton agent, is not a virus, as had been surmised, but is a pleuropneumonia-like organism (PPLO), resembling the L forms of bacteria, which also grow without a rigid cell wall.

Because of the growing recognition that PPLO may be important agents of disease in humans as they have been known to be in lower animals, the Laboratory of Bacteriology is beginning to cultivate various PPLO forms in culture media. To further explore the relationship of PPLO to diseases in humans it is essential that means of cultivating and identifying the organisms be improved and that better antigens and techniques for quantitating the immune response be developed.

Highlights of bacterial research by the Institute, reported upon elsewhere in the record of these hearings, include epidemiological information about forms of resistant staphylococci present in a large hospital; the first direct observation of cell wall growth of *Streptococcus pyogenes*; case-finding of new bacterium "II-D" implicated in subacute bacterial endocarditis; reports on possible effects of urine acidity on chemotherapy of stubborn urinary-tract infections; efforts

to improve tuberculosis immunization through experiments employing purified antigen in rabbits.

ENCEPHALITIS

Sporadic outbreaks of viral encephalitis in various areas of the United States pose a problem of major public health significance. With the aid of a research grant of \$186,000 awarded by the National Institute of Allergy and Infectious Diseases, the Florida State Board of Health has launched an investigation of encephalitis in the Tampa Bay area. Three outbreaks of the insect-borne viral infection have occurred in the Tampa Bay area in recent years: in 1959, with 63 cases and 5 deaths; in 1961, with 25 cases and 7 deaths; and in 1962, with 158 cases and 19 deaths. St. Louis encephalitis (SLE), or a closely related virus, has been identified as causing the acute form of the disease, characterized by inflammation of the brain and spinal cord.

The director of the encephalitis research project, Dr. James O. Bond, of the Florida State Board of Health, announced the objectives of the study are to determine how and where the SLE virus exists in wildlife, and to determine the modes of transmission to man. Hopefully, this may lead to the development of new and more effective measures for containment of the infection. Dr. Bond has noted that man actually may be the accidental victim of the virus, since it is believed to be transmitted by mosquitoes that have bitten infected birds harboring the disease.

In addition to the Florida State Board of Health, whose facilities are being fully mobilized for the study, institutions in other States will participate on a cooperative basis. Dr. Bond pointed out that opportunities exist for important related studies on insect-borne diseases, and every effort will be made to work with those research groups that have an interest in the problem and would like to assist in its solution. Through intensive research efforts such as these, new information should be gained which may result in the ultimate elimination of this disease potential.

GERM-FREE ANIMAL RESEARCH AND VIRUS-FREE ANIMALS

Although Louis Pasteur theorized in 1885 that life in a germ-free environment might be impossible, modern-day research with animals reared in an environment free of contaminating micro-organisms is proving not only that life is possible without germs but also that this condition of existence provides clues to basic immunologic processes, the nature of resistance to disease. Also, individual micro-organisms can be observed in the germ-free animals to determine the pathogenicity of a single kind of microbe without confusing interaction by other kinds. On the other hand, the interaction of combinations of germs can be purposely observed to see if the presence of one organism encourages the infectious processes of another.

The largest facility at NIH for the study of germ-free animals is maintained in the Laboratory of Germfree Animal Research by the National Institute of Allergy and Infectious Diseases, where 20 stainless-steel isolators are employed to provide the animals needed for various research projects and for the conduct of experiments in a germ-free environment.

For example, evidence that intestinal bacteria play a role in altered susceptibility of female mice to parasitic infection was obtained through studies by the Laboratory of Germfree Animal Research. Female mice are characteristically more resistant than males to a worm parasite, *Nematospiroides dubius*; but this difference did not exist in the germ-free females. The absence of bacteria in germ-free females resulted in their being no more resistant to the worm infection than males. Sex difference in resistance to certain infections, including parasitic, has been known for some time in a variety of diseases, the female having the lighter and more short-lived infection. In parasite infestations many factors may be involved, including differential effects of male and female sex hormones on the parasite. The study cited gives the first indication that the presence of bacterial flora may be involved in the phenomenon of greater resistance of female mice to parasitic infection.

In a grant-supported study at the Lobund Laboratory, University of Notre Dame (where germ-free research was pioneered), nutritional aspects of germ-free animal research are being considered. The work supported here has a two-fold purpose: (1) to develop additional strains of germ-free mice, guinea pigs, and rabbits, which are especially needed for virus and cancer research, and (2) to improve the germ-free animal as an experimental tool by rearing

it from birth on diets that are chemically defined and are antigen low. There is a real need for this type of animal for studies of natural resistance.

In order to raise newborn germ-free animals on artificial formulas, profound knowledge is required of the nutritional requirements and of the physiology and chemistry of digestion. Dr. Wostmann and his coworkers have reported substantial progress in developing new diet formulas on which certain germ-free strains attain normal growth and maturation. Germ-free rabbits, for example, have conceived and born litters for the first time.

Virus-free animals

Scientists of the Institute's Laboratory of Germfree Animal Research now are turning their attention to the behavior of viruses, the smallest of microorganisms, in the germ-free host. A comparison of the relative susceptibility of conventional and germ-free mice as well as possible interactions among bacteria and viruses are being observed. Virologists of the Laboratory of Infectious Diseases aid this research by conducting periodic tests of specimens from the mouse colony to make certain that viruses cannot be cultured or detected by reagents.

NEPHROSIS

Nephrosis is a chronic, progressively degenerative disease of the kidneys. Certain forms of the disease are now believed to be caused by autoimmune reaction. This means that antibodies, ordinarily manufactured by the individual's defensive machinery to ward off infection, are somehow formed and wage civil war against vital parts of the body, such as the kidneys and connective tissues. In addition to nephrosis, the group of disorders that fall into that category of "self-generated" illness includes systemic lupus erythematosus, thyroiditis, and some anemias and encephalitides.

This Institute's Laboratory of Immunology, in collaboration with the Laboratory of Clinical Investigations, has been conducting studies of various kinds of therapy in patients with the nephrotic syndrome. One of the more promising substances tested in a drug called 6-thioguanine (6-TG), a derivative of the chemical compound, purine. 6-TG is called an antimetabolite because it suppresses the normal metabolic activity in the cell. When administered to a limited number of nephrosis patients who had been formerly treated with steroid drugs, 6-TG was shown to have a definite therapeutic effect in some patients. Not only did it suppress the antibody response, but it appeared to have a continuing effect on the mechanisms for maintaining "normal" levels of gamma globulin, the blood fraction which carried the antibodies.

Results of this study indicate that purine antimetabolites offer promising alternatives to the use of corticosteroids in the treatment of nephrosis, and possibly in the treatment of other diseases associated with autoimmune phenomena. Moreover, the study suggests the possibility of determining exactly how these drugs act upon the body.

THE ROCKY MOUNTAIN LABORATORY

The Rocky Mountain Laboratory of the National Institute of Allergy and Infectious Diseases is located in Hamilton, Mont., in the Bitterroot Valley, where Rocky Mountain spotted fever was particularly virulent. Established in 1921 to bring this fever under control, the Laboratory has become a world center for research on animal diseases transmissible to humans, on the immunologic response to such infections, and on animal diseases which can be used as prototypes of little understood infectious processes, such a viremia leading to chronic illness. The Rocky Mountain Laboratory researchers are in a strategic position to conduct field studies of problems ranging from bat rabies to overwintering of encephalitis virus in snakes, and of fungi that thrive in desert climates. The Hamilton, Mont., research center has evolved from a few cabins, the center for spotted fever studies, to a modern-day, \$3 million research complex investigating some of the major public health problems of the Northwestern region and of the Nation.

RELATIONSHIP OF ALLERGIES TO INFECTIOUS DISEASES

Mr. DENTON. I just want to ask you a few questions.
What is an allergy?

Dr. ANDREWS. An allergy is a sensitization to a particular substance. One has to distinguish between poisons and allergens. Poisons affect everybody in about the same way. For example, everybody receiving a dose of cyanide would die. But with an allergen you will find that certain individuals are hypersensitive to particular substances, such as lacquer; other persons are not. There is never complete sensitization for everyone.

Mr. DENTON. Something that they eat, or smell, or are close to?

Dr. ANDREWS. This can be something with which they have been in contact; something which they eat; something which they breathe.

Mr. DENTON. What is the connection between that and infectious diseases?

Dr. ANDREWS. Infectious diseases are caused by living organisms such as bacteria or by some nonvital organisms, such as viruses, and by animal parasites, so that there is a multiplicative process involved with disease-causing organisms.

Mr. DENTON. I do not see the connection between allergy and infectious disease.

Dr. ANDREWS. There is a very substantial connection as far as these two types of diseases are concerned.

Mr. DENTON. Why are they in the same institute?

Dr. ANDREWS. I think Dr. Shannon should answer that.

Dr. SHANNON. I think the problem here, Mr. Denton, is that the body's response to an infectious agent, whatever it may be—or the body's response to a foreign chemical uses precisely the same mechanism. This is the so-called immunological response. In the one case, the body reacts to the infectious agent by building up what is called an immune body, or an antibody. This, in turn, interferes with the development of the invading organism, and the organism is presumably conquered, and the disease is stopped.

Mr. DENTON. This does not happen in allergy; does it?

Dr. ANDREWS. No, sir. That is just the point.

The same mechanisms in general, in the normal individual, will handle foreign protein—foreign substances—in precisely the same way, but the disease of asthma or the disease of any one of the other allergic manifestations, comes as a result of the inability of these body-defense mechanisms to handle it in the normal fashion, and it is this inability that results in the formation of byproducts that produce the symptoms of disease.

Mr. DENTON. For instance, ragweed causes hay fever.

Dr. ANDREWS. Yes.

Mr. DENTON. Now, does the normal person have some antibody that takes care of that?

Dr. ANDREWS. The normal person can take the protein, digest it, dispose of it without any trouble at all.

RELATION OF INSTITUTE AND CDC WORK

Mr. DENTON. Now, what is the difference between your work on infectious diseases and the work of Communicable Disease Center?

Dr. SHANNON. The Communicable Disease Center is similarly concerned with infectious disease, but primarily, their role is one of a supporting role to the public health programs in the United States. This is the application of knowledge to the disease situation as it occurs in the States. Dr. Andrews is concerned with the development of new knowledge. Now, this is an obvious, necessary, and desirous overlap because, otherwise, these two laboratory groups would not interact, one with the other.

Mr. DENTON. But it does do research, does it not?

Dr. SHANNON. Yes, sir. This is the area of overlap.

Mr. DENTON. As a matter of fact, you transferred about \$11½ million from this agency to the Communicable Disease Center.

Dr. SHANNON. Yes, sir. Very frequently, there will occur times when we are asked to do something requiring facilities and resources which are at CDC. By arrangement, then, they will do these things for us, rather than us setting up comparable, parallel mechanisms to do that. There is a very close working relationship between the two organizations that provides (1) the desirable overlap, and (2) prevents the undesirable duplication.

Mr. DENTON. Now, most of your increase is due to research?

Dr. ANDREWS. Yes, sir.

Mr. DENTON. You have 10 new employees; 7 in direct research, and 3 are reviewing grants.

I think that is all.

Mr. FOGARTY. Thank you, Doctor. We will recess until 1:30.

DEATHS, DISABILITY, AND COST OF ALLERGY AND INFECTIOUS DISEASES

Statistics of the annual number of deaths and total current number of reported illnesses caused by selected diseases dealt with in the National Institute of Allergy and Infectious Diseases, and the estimated annual cost to the Nation are presented in table I.

Deaths attributable to allergic, infectious, and parasitic diseases during 1960 are used since National Office of Vital Statistics advises only preliminary data are available for 1961. Since most of these conditions cause illness rather than death, morbidity is presented for 1961 to reflect the extent of impairment created by these diseases. The following table illustrates the above and reports only those deaths and cases which are diagnosed by a reporting laboratory or a qualified physician, health officer, or other professional person.

TABLE I

Category	Reported deaths, 1960 ¹	Reported cases, 1961
Allergic diseases:		
Asthma.....	5,394	
Other allergic disorders.....	97	
Infectious and parasitic diseases:		
Bacterial diseases:		
Scarlet fever and streptococcal sore throat.....	108	338,410
Septicemia and pyemia.....	1,920	
Tuberculosis.....	10,866	53,727
Venereal diseases:		
Syphilis.....	2,945	124,658
Gonorrhea.....	38	264,158
Other.....	15	2,466
Viral diseases:		
Acute upper respiratory infections (includes common cold).....	911	
Influenza.....	7,872	² 180,856
Hepatitis.....	938	72,651
Measles.....	380	423,919
Poliomyelitis, acute.....	230	1,312
Unspecified bacterial and viral diseases:		
Bronchitis.....	4,343	
Dysentery, all types.....	³ 355	⁴ 12,571
Meningitis, all types.....	2,960	
Pneumonia, all types.....	58,931	² 12,439
Infections of the kidneys.....	7,645	
Infections of the newborn.....	4,786	
Infections of the skin.....	632	² 405,997
Other bacterial and viral diseases.....	4,539	
Fungal diseases: All types.....	357	
Parasitic diseases:		
Amebiasis and other protozoal diseases.....	88	⁵ 2,850
Hookworm and other worm diseases.....	66	⁶ 11,255
Total reported.....	116,416	1,907,269

¹ Reported deaths, all causes, totaled 1,711,982 in 1960.

² Incomplete reporting. Only certain States and/or cities require reporting of this item.

³ Does not include 7,539 deaths ascribed to gastroenteritis and colitis.

⁴ Includes shigellosis only.

⁵ Only amebiasis reported.

⁶ Only hookworm reported.

Data regarding certain specific diseases of interest to the National Institute of Allergy and Infectious Diseases are not available. Of particular interest in this connection are staphylococcal infections, which are distributed among several of the entries in attached table, particularly septicemia and pyemia, infections of the kidney, infections of the newborn, and infections of the skin.

Table II presents estimates of the incidence (number of cases per year) associated disability, and cost to the Nation for the allergic, infectious, and parasitic diseases. Figures for the annual cost to the Nation include only the value of time lost from work due to disability. Statistics are not available to include the cost of medical and hospital care, drugs, and compensation specifically attributable to these diseases.

TABLE II.—*Allergic, infectious, and parasitic diseases—number of cases, associated disability, and cost to the Nation for the period July 1, 1960 to June 30, 1961 (unless otherwise noted)*

[Data (unless otherwise noted) from various issues of the series "Health Statistics From the U.S. National Health Survey," Division of Public Health Methods, Public Health Service]

	Number of cases	Restricted activity (days)	Bed disability (days)	Work loss (days)	School loss (days)	Average daily number of persons with restricted activity	Annual cost to the Nation ⁵
Total respiratory conditions-----	196, 276, 000	631, 388, 000	267, 945, 000	1 117, 943, 000	1 99, 951, 000	1, 757, 231	1 \$2, 219, 215, 000
Upper respiratory conditions: Common cold, sinusitis, pharyngitis, tonsillitis, laryngitis, tracheitis-----	138, 735, 000	385, 926, 000	144, 309, 000	-----	-----	1, 057, 332	-----
Other respiratory conditions: Influenza, pneumonia, bronchitis (acute), pneumoconiosis, emphysema-----	57 541, 000 49, 057, 000	245, 462, 000 225, 373, 000	123 636, 000 107, 716, 000	----- 1 17, 249, 000	----- 1 41, 410, 000	699, 899 617, 460	----- 1 324, 357, 000
Other infectious and parasitic diseases-----	2 1, 009, 000	3 96, 533, 000 4 28, 560, 000	3 30, 022, 000	4 31, 000, 000 4 11, 000, 000	-----	3 264, 529 4 78, 247	4 538, 656, 000 191, 136, 000
Allergic diseases: Asthma and hay fever-----	-----	-----	-----	-----	-----	-----	-----
Other allergic disorders-----	-----	-----	-----	-----	-----	-----	-----
Total-----	246, 342, 000	981, 854, 000	405, 083, 000	177, 192, 000	141, 361, 000	2, 147, 467	3, 273, 364, 000

¹ For the period July 1, 1959, to June 30, 1960.

² For the period July 1, 1959, to June 30, 1961.

³ For the period July 1, 1957, to June 30, 1958.

⁴ Nachtigall, H. B., "Compensatory Medicine," 9: 5, 1957; and "Health in California," Department of Public Health, State of California, 1957. Both reflect surveys made before 1957. More recent data are not available.

⁵ Includes only value of time lost from work, calculated on the Department of Commerce 1960 estimate of \$4,704 average annual earnings per full-time equivalent employee and on a 40-hour workweek, 50 weeks per year.

HIGHLIGHTS OF PROGRESS IN RESEARCH ON ALLERGY AND INFECTIOUS DISEASES, 1962

Items of interest on program developments and research studies conducted and supported by the National Institute of Allergy and Infectious Diseases

VIRUS DISEASES AND PPLO

EATON AGENT REVEALED AS PLEUROPNEUMONIA-LIKE ORGANISM

Eaton agent, tentatively classified as a virus since its discovery in 1944, has been grown for the first time in a cell-free medium and identified as one of the obscure subbacteria known as pleuropneumonia-like organisms (PPLO). An important cause of pneumonia, this is the first PPLO linked with human disease. The research is reported by Dr. R. M. Chanock, Laboratory of Infectious Diseases; Dr. Leonard Hayflick, Wistar Institute of Anatomy and Biology, Philadelphia; and Dr. M. F. Barile of the Division of Biologics Standards in the January 1962 "Proceedings of the National Academy of Sciences."

In the present study, infected culture fluid was prepared at the National Institutes of Health and sent to the Wistar Institute where it was grown on agar plates in an acellular medium. Appearance of colonies on the agar plates and other properties described in the report definitely established the organisms as PPLO. Fluorescent antibody studies confirmed them as Eaton agent.

The identification of Eaton agent as a PPLO represents not only a step toward diagnosis and prevention of atypical pneumonia, which it is known to cause, but also implicates PPLO in a significant proportion of respiratory disease of children and adults. Previously, PPLO have been related only to disease in animals, particularly cattle. The researchers believe that attempts to recover human types of PPLO should be included in any systematic investigation of the presently unexplained segment of human respiratory disease.

The investigators believe that once the optimum conditions for growth of Eaton agent on agar have been defined, it is possible that recovery of the agent and its identification by immunofluorescence could be achieved within a few days, thus providing a rapid method for diagnosis of infection.

This work resolves the longstanding puzzle of the status of Eaton agent, previously considered to be an atypical virus. Its sensitivity to streptomycin and various tetracycline derivatives, established by Dr. Chanock and coworkers last year in a study of primary atypical pneumonia in Marine recruits, becomes understandable in the light of the new knowledge of Eaton agent as PPLO.

Previously, Dr. Chanock and his associates had also observed that naturally acquired antibody offered protection against Eaton agent illnesses. The fact that antibodies are effective against Eaton agent indicates that a protective vaccine may eventually be developed. Growth of the agent on artificial medium should stimulate efforts to prepare vaccines.

LONG-TERM STUDY AT JUNIOR VILLAGE SHOWS LARGE AMOUNT OF RESPIRATORY ILLNESS

Findings of a "comprehensive, long-term, clinical epidemiologic and laboratory study of acute infections and illnesses as they occurred naturally in nursery babies at Junior Village," are reported in the American Journal of Hygiene. These include isolation of nearly 60 immunologically different viruses and association of at least 10 virus serotypes with respiratory illness.

Dr. Joseph A. Bell of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases is senior author of the study. A total of 587 children reside in the nursery group during the first 3 years of the study, which was initiated in 1955. This population was continually changing. "The intensity of study observations and the continual flow of new children into the nursery group have contributed to finding a surprisingly large number of illnesses and infections."

Among the findings during the first 3 years of the study are:

"On the average, each child had one new febrile illness every 3 weeks and a new bacterial or virus infection every 2 to 4 weeks.

"To date, nearly 60 immunologically different viruses have been isolated, many of which were heretofore unrecognized or unclassified.

"At least 10 virus serotypes have been associated with illness in such a manner that their etiologic role is highly probable."

The reports include the description of four previously unrecognized adenoviruses, as well as ECHO viruses, myxoviruses, and parainfluenza viruses. A number of bacterial agents were also associated with respiratory disease by the study.

Associated with Dr. Bell in the study are Dr. Robert J. Huebner, Dr. Leon Rosen, Dr. Wallace P. Rowe, Dr. Roger M. Cole, Dr. Robert M. Chanock, and Ruth Shvedoff, all of the Laboratory of Infectious Diseases, NIAID; Dr. Thomas M. Floyd of the National Naval Medical Center; and Dr. Francis M. Mastropa, formerly of the National Institutes of Health.

MEASLES VACCINE STUDIED IN CHILDREN WITH CYSTIC FIBROSIS AND LEUKEMIA

The danger of measles in children with either cystic fibrosis or acute leukemia has been noted. A number of cystic fibrosis patients have shown progressive declines in their general condition with exacerbations of their pulmonary infections and an early termination after contracting measles. Infection with measles virus in children with acute leukemia has occasionally terminated fatally and, at autopsy, pathological changes characteristic of giant-cell pneumonia were present. Accordingly, two research groups, supported by the National Institute of Allergy and Infectious Diseases, have investigated the possibility of protecting these unusually vulnerable patients by vaccination with attenuated measles virus vaccine. The results of both studies appear in the *American Journal of Diseases of Children*.

The first group, Drs. Harry Schwachman, Samuel Katz, and Lucas L. Kulczycki of the Children's Hospital Medical Center, Boston, administered the vaccine to 200 children with cystic fibrosis, varying in age from 7 months to 14 years. No unfavorable reaction occurred in 75 of the children. The recorded reactions included fever in 113 patients, rash in 59, cough in approximately 40, and a small number of minor complaints such as listlessness, anorexia, and headache. Titers determined in 57 patients 1 month or more after vaccination demonstrated significant rises in most cases. Those who showed the poorest response were checked for neutralizing antibodies. In six cases tested, only one failed to show a satisfactory rise.

Drs. Anna Mitus, Ann Holloway, Audrey E. Evans, and John F. Enders, also of the Children's Hospital Medical Center, vaccinated 12 acutely leukemic children, of whom 8 were probably susceptible to measles according to their histories and lack of complement fixing antibodies. After vaccination, four developed measles antibodies, two did not, and two exhibited delayed responses, suggestive of depression of resistance. Considering these possibly abnormal antibody responses, and the development of giant-cell pneumonia in one of the patients exhibiting a delayed response, the administration of the vaccine to children with acute leukemia is, in the authors' view, contraindicated at present.

INTERFERON ALTERS CELLULAR RESISTANCE TO SINDBIS VIRUS IN MIXED CULTURES

Drs. Ion Gresser and J. F. Enders, of Harvard Medical School, grantees of the National Institute of Allergy and Infectious Diseases, observed by chance that in mixed cultures of primary human amnion (HA) cells and continuous line human amnion (WS) cells response to Sindbis virus was strikingly altered from that in pure cultures of either HA or WS. They report in *Virology* that interferon appears to be responsible for this effect.

Sindbis virus, named for the Nile Delta district of its discovery in 1952, has been isolated from mosquitoes, mites, and birds, but not man. In this study, Sindbis-infected primary cultures of HA cells alone were completely destroyed as the virus multiplied. Moderate amounts of virus added to WS cell cultures alone produced no degenerative effect nor could complete virus multiplication be demonstrated. Cell destruction did occur at high viral concentrations. When a small number of WS cells were added to primary cultures of HA cells, the HA cells were not destroyed.

The investigators believe that the Sindbis virus stimulated the WS cells (either in pure or in mixed culture) to produce large amounts of interferon which inhibited the usual destructive effect of this virus in HA cells. Occasionally, WS cells were destroyed when too few of them were added, and some

of the HA cells were also destroyed before sufficient protective interferon became available.

In the system studied, interferon in high concentrations rapidly appeared after virus inoculation. Interferon protection of HA cells was indicated by marked decrease or absence of cell degeneration even after challenge with several thousand infecting doses of virus, by a decrease in the number of infected cells, and by reduction in the titer of infectious virus. No other factors to account for the protection apparently conferred by WS cells were found.

Accumulating knowledge about variations in production of interferon in the test tube leads the investigators to speculate that variations within the tissues of living organisms may help determine different responses to viral infection. Interferon produced by relatively resistant cells in proximity to susceptible cells may explain localization of lesions of virulent poliovirus in the central nervous system or influenza virus in the respiratory tract.

SIMPLIFIED TECHNIQUE MAKES POSSIBLE RAPID IDENTIFICATION OF VIRUS

Rapid identification of herpes virus has been made possible by simplified preparative techniques. Experimenters find that specimens from human lesions can be prepared, examined, and counted within 3 hours, permitting a rapid presumptive identification.

In diagnosing a 43-year-old patient ill with a disease resembling generalized herpes and with a history of Hodgkin's disease, Kendall O. Smith and Joseph L. Melnick of Baylor University identified the pathogen in less than 3 hours by staining and direct examination under an electron microscope. In contrast, the tests hitherto used, involving cytopathogenic effects of the virus, are not indicative for 24 hours. The new method, described in *Science*, was developed with the aid of a postdoctoral fellowship from the National Institute of Allergy and Infectious Diseases and a grant from the National Cancer Institute.

LIZARD IS POSSIBLE HOST FOR ENCEPHALITIS VIRUS

The presence of eastern equine encephalitis hemagglutination inhibition antibody found in wild lizards, following equine outbreak of EEE in Panama, implicates this animal as a reservoir for the disease.

Between October 1958 and April 1960, wild lizards were collected on several Panamanian ranches where an outbreak of EEE had occurred in July 1958. When sera of 246 lizards were tested, substances inhibiting hemagglutination by EEE virus antigen were found in about 14 percent, suggesting previous infection with EEE. The investigators, Drs. John E. Craighead, Alexis Shelokov, and Pauline H. Peralta of the Laboratory of Tropical Virology, National Institute of Allergy and Infectious Diseases, report their results in the *American Journal of Hygiene*.

Studies on EEE virus have failed to explain how it is maintained and disseminated in nature. It now appears likely that small vertebrate animals serve as reservoirs since there is little evidence to suggest that the virus survives for indefinite periods in the arthropod vector. Although birds and rodents may play a role in the natural history of the virus, only the lizard has provided laboratory evidence for a significant role to date. The authors caution that conclusive proof of the lizard's role must await the recovery of the virus from naturally infected animals.

RABID BATS CONSTITUTE ACTUAL AND POTENTIAL PUBLIC HEALTH PROBLEM

A 7-year study of bat rabies in Montana has resulted in the delineation of a potential public health problem of major significance. The problem has two aspects: (1) the actual and potential spread of rabies from bats to man; and (2) the transmission of the virus to wild animals and livestock. Six human cases of rabies in the United States have been attributed directly to bats and the increase of rabid bats constitutes a very real danger. Transmission to other animals, an equally dangerous potential source of human infection, has not yet been demonstrated in Montana, but may possibly be the source of sporadic rabies in dogs, cats, foxes, skunks, and raccoons in Florida.

Since the isolation of rabies virus from a bat in western Montana in 1954, Drs. J. Frederick Bell, G. John Moore, George H. Raymond, and C. E. Tibbs of the Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases, collected several thousand bats representing almost all species known to occur in Montana and examined them for rabies virus. Their report appears in the *American Journal of Public Health*.

Over a period of 7 years, rabies virus was demonstrated by the oral swab method in 21 bats of 8 species. This indicates a very high incidence of rabies probably exists in the bat population. Six of the infected bats were tested for ability to transmit virus by bite and five did so on one or more occasions. Many of the bats showed outward evidence of infection such as confusion, incoordination, or aggressiveness.

Virus was not limited in distribution to the central nervous system and salivary glands, but was also found in brown fat and in several other tissues.

ASIAN INFLUENZA ENDEMIC IN NEW YORK AFTER 1957 PANDEMIC

Supported by an influenza special research grant from the National Institute of Allergy and Infectious Diseases, investigators at the New York Hospital-Cornell Medical Center have been engaged in an attempt to characterize the nature of Asian influenza in the postpandemic period.

In the light of evidence that continuing infection with this influenza virus has occurred in the absence of epidemic disease in the community, Drs. Donald Kaye, Michael Rosenbluth, Edward W. Hook, and Edwin D. Kilbourne studied 49 patients either with illnesses suggestive of influenza or exhibiting roentgenographic evidence of pulmonary infiltration.

During the period of study, 20 patients had influenza caused by the A2 virus. This was proven either by virus isolation, antibody studies, or both. Of the 20 patients, 13 were females and 7 males. Their ages ranged from 20 to 75 years. Uncomplicated illnesses typical of the disease were observed in 12 of the patients, 3 were classified as having pulmonary syndromes, 4 had mild cases of segmental influenza virus pneumonia, and 1 was observed too briefly for classification.

The authors also concluded that statements concerning the virulence or avirulence of influenza virus must be evaluated in relation to the presence or absence of underlying cardiopulmonary disease in the victim. They state further that the virulence of influenza A2 virus appears to be unaltered.

The study was reported in the American Review of Respiratory Diseases.

PARAINFLUENZA 2 VIRUS SHOWN TO BE ETIOLOGICALLY RELATED TO THE CROUP SYNDROME

Findings reported in Pediatrics constitute the first "evidence from controlled epidemiologic studies that parainfluenza 2 virus is etiologically related to the croup syndrome. The studies were supported by the National Institute of Allergy and Infectious Diseases, and were conducted at Children's Hospital, Washington, D.C., by Dr. Hyun Wha Kim, a U.S. Public Health Service fellow. Investigators at the hospital, as well as from Georgetown University and NIAID's Laboratory of Infectious Diseases, collaborated in this work.

During the 3-month period of the study, parainfluenza 2 virus was recovered from 7 of 28 patients with croup. Serologic tests indicated that three other patients were infected with this agent. In contrast, this virus was isolated from only 3 of 470 patients with respiratory illness other than croup or with no respiratory illness.

The parts played by parainfluenza 1 and 3 viruses in respiratory diseases of children have been emphasized in previous NIAID studies. Dr. Kim states that on the basis of the current study, parainfluenza 2 can properly assume a place with parainfluenza 1 and 3 viruses as important agents in these diseases. He also notes that 71 percent of the patients with croup in this study were infected with one of the parainfluenza viruses.

This finding alone, the investigator states, "would probably warrant inclusion of the parainfluenza viruses in a vaccine intended for immune prophylaxis against respiratory tract infections in young children. Although there is accumulating evidence that reinfection with these viruses is possible, initial infection occurs early in life and is often accompanied by relatively severe infection of the lower respiratory tract. Thus the major value of such a vaccine would probably be the prevention of such serious syndromes as croup and viral bronchopneumonia in infants and young children."

WESTERN ENCEPHALITIS VIRUS RECOVERED IN MASSACHUSETTS

Isolations of WE virus from mosquitoes, a chicken, and a pheasant provide the first clear-cut demonstrations of active infection with this virus in Massa-

chusetts, the second State east of the Appalachians in which it has been reported.

Dr. Richard O. Hayes, of the Communicable Disease Center Taunton Field Station, and Mrs. Joan B. Daniels and Dr. Robert A. MacCready, grantees of the National Institute of Allergy and Infectious Diseases, report their findings in the Proceedings of the Society for Experimental Biology and Medicine. The grantees are on the staff of the Massachusetts Health Research Institute, Inc.

WE virus was isolated from 26 pools of *Culiseta melanura* and one pool of *Aedes canadensis* mosquitoes collected in 1959. It was also obtained from the brain of a 3-year-old Impeyan pheasant on a wild animal farm, and from the blood of a 3-week-old chicken. Additional isolations in the State were made in 1961 from mosquitoes and from a catbird.

Antibodies to WE and to eastern encephalitis (EE) were detected in domestic fowl hatched and reared in widely separated areas in eastern Massachusetts in 1959.

The virus of WE is responsible for the majority of human and equine arthropod-borne encephalitis in North America, but it has not been associated with known human disease along the eastern seaboard. Heretofore its insignificance as a cause of disease has been attributed to the lack of a vector as efficient as the *Culex tarsalis* mosquito of the West. Evidence is accumulating, however, that *Culiseta melanura* is an enzootic vector of both WE and EE in the Eastern United States.

ALLERGY-IMMUNOLOGY

DEFINITE SEQUENCE OF REACTION TO INSECT BITES DEMONSTRATED EXPERIMENTALLY

Characteristic skin reactions follow injection of specific antigens into the skin of immune subjects. Delayed hypersensitivity occurs in early immunity when antigen causes swelling and redness in 24-48 hours, persisting 72 hours or longer. Later, when circulating antibodies are present, an immediate reaction occurs in 4-12 hours, then rapidly disappears. Continued exposure to antigen may result in desensitization, in which there is no visible response to intradermal injection.

Drs. E. Benjamini, B. F. Feingold and L. Kartman of the Kaiser Foundation Research Institute, the Kaiser Foundation Hospital, San Francisco, and the San Francisco Field Station Technology Branch of the Communicable Disease Center, PHS, report a study on the stages of skin reactivity to flea bites. Their work, supported in part by a grant from the National Institute of Allergy and Infectious Diseases, is reported in the current Proceedings of the Society for Experimental Biology and Medicine.

Three groups of guinea pigs (five in each) were sensitized daily to bites of cat fleas. Delayed skin reactions occurred in 5-6 days. The animals were then exposed twice per week for about 14 weeks. These animals responded to conducted exposure to the antigen (flea bites) in five stages: (1) induction of sensitivity, (2) predominantly delayed skin reactivity, (3) combination of delayed and immediate reactions, (4) predominance of immediate response, and (5) nonreactivity. This pattern coincides with current theory about human reaction to insect bites.

Controls were sensitized by daily flea bites. After delayed and immediate skin reactions occurred, groups of animals were then challenged at 3, 6, 12 and 18 months. They responded to challenge with both immediate and delayed skin reactions, indicating that under these conditions hypersensitivity persisted at least 12 to 18 months.

The authors believe that repeated exposure to the material introduced by the flea bites caused the experimental animals to become desensitized. When that state was established, periodic challenge revealed relative desensitization that persisted for at least 5 months.

These studies are significant because of applicability to problems of insect control. They also correlate with current immunological concepts holding that delayed hypersensitivity is a primitive stage of the immune reaction usually terminating in antibody development and immediate hypersensitivity. The production of this sequence by a natural biological mechanism is important. Results also suggest that practical methods can be developed in man to alleviate allergy to insects.

PRECIPITIN TEST IMPLICATES MILK ALLERGY IN INFANT ILLNESSES

A previous study illustrating the benefits of withdrawal of native milk proteins from 7 pediatric patients with milk precipitins in their sera stimulated National Institute of Allergy and Infectious Diseases grantee Dr. N. H. Holland and associates at the University of Cincinnati College of Medicine to examine serum specimens from 1,618 infants and children by immunoelectrophoresis. They found milk precipitins present in 87. The great majority of serum specimens were from hospitalized children. Observing the 87 ill children with measureable precipitating antibodies to milk, the researchers found a higher incidence of recurrent respiratory tract disease, anemia, failure to thrive, and enlarged liver and spleen than was present in a control group of 87 other hospitalized children without precipitins, matched for age to the study group and picked at random.

The University of Cincinnati grantees followed the progress of 24 of the precipitin-positive children treated by withdrawal of pasteurized milk for periods varying from 4 months to over a year. Twenty-two (91 percent) benefited markedly. In 12 of 17 with recurrent or persistent respiratory tract disease improvement was striking, with no recurrence of pneumonia, bronchitis, asthma, or upper respiratory disease. Enlargement of liver disappeared in all eight children so affected. Spleen enlargement also disappeared in six of seven cases. Unexplained fevers and enlarged lymph glands were among the conditions which also disappeared when the diet was changed. Only 2 of 24 children did not respond to the different diet.

The authors believe that despite "the inherent shortcomings of the method of evaluation," patients with the symptoms in the report, plus demonstrable precipitins to milk, should have native milk protein removed from their diet. Since the precipitins in these patients were directed primarily toward the bovine serum proteins, which are nonantigenic in some processed milks, substitution of evaporated milk for pasteurized or homogenized milk should, in most cases, offer therapy as effective as milk substitutes such as soybean milk, meat base, or hydrolyzed proteins.

The study was reported in the *Journal of Pediatrics*.

LONG-TERM STUDY CONFIRMS HIGH SPECIFICITY OF KVEIM TEST IN DIAGNOSIS OF SARCOIDOSIS

The results of a 15-year study at Mount Sinai Hospital, New York City, supported by the National Institute of Allergy and Infectious Diseases, confirm the high specificity of the Kveim test—devised independently 20 years ago by Kveim and Nickerson for the diagnosis of sarcoidosis, a chronic tissue disease of uncertain etiology. This test provides histologic corroboration for diagnosis, as recommended by 1960 International Conference on Sarcoidosis.

Dr. Louis E. Siltzback reports in the *Journal of the American Medical Association* that in a series of 750 patients, 311 of whom were eventually found to have sarcoidosis, the intracutaneous Kveim test proved to be an important aid in the early and accurate diagnosis of sarcoidosis. The sarcoidal tissue, preferably spleen, is obtained aseptically; the suspension is heat-treated and preserved with phenol. With validated sarcoidal tissue suspension, positive microscopic reactions consisting of granuloma formation at the injection site after 4 to 6 weeks were observed in 84 percent of patients with biopsy-confirmed sarcoidosis. Two patients among a group of 313 patients with diseases other than sarcoidosis showed false positive reactions.

The nature of the active principle in sarcoidal tissue which evokes the granuloma of a positive Kveim reaction is not known. Preliminary histochemical studies by the grantees have established the presence of neutral and acid mucopolysaccharides, phospholipids, and acid phosphatase in the granuloma of the patient's affected tissues and in the induced granuloma at the Kveim test site. It is therefore not unlikely, according to the report, "that the test suspensions contain the same material which is responsible for the granuloma found in the tissues of patients with sarcoidosis. Isolation of the active principle responsible for the positive Kveim reaction would illuminate the pathogenesis of sarcoidosis and perhaps also the etiology of this disorder."

PARASITIC DISEASES

NEW ANTIMALARIAL DRUG GIVES LONG-LASTING PROTECTION IN CLINICAL TRIALS

A single injection of a new drug given volunteers nearly a year ago is continuing to protect them from malaria induced by heavily infected mosquitoes which have been allowed to bite them at monthly intervals. Other volunteers not given the drug invariably come down with malaria after being bitten by these mosquitoes.

Results of clinical trials of the long-lasting antimalarial, which thus far has been protective nearly 10 times longer than conventional suppressives, were reported to members of the American Society of Tropical Medicine and Hygiene meeting at Atlanta, Ga., by Dr. G. Robert Coatney of the National Institutes of Health, research bureau of the Public Health Service. He reported remarkable initial success with the new experimental drug, designated as CI-501.

Developed by scientists at Parke, Davis & Co., Ann Arbor, Mich., CI-501 is an experimental drug, not yet available for general use. It was supplied by the company to Dr. Coatney and his associates, Drs. Peter G. Contacos, Harvey A. Elder, and Mr. John W. Kilpatrick for clinical testing with volunteer patients. Parke, Davis & Co., investigators and scientists at Christ Hospital Institute of Medical Research, Cincinnati, Ohio, also reported to the meeting on laboratory and animal work with the new antimalarial.

If the promise of initial trials in volunteers is borne out under actual field conditions, the CI-501 compound should greatly increase the chances of success in worldwide malaria eradication efforts. The United States plays a major role in the program to eliminate this disease, which afflicts 200 million people and kills 2 million each year.

FIRST RELIABLE SEROLOGIC TEST DEVELOPED FOR INVESTIGATION OF MALARIA ANTIBODY PRODUCTION

No reliable serological test has been available in the past to follow the course of antibody production in malarial infections. Preliminary results from a human volunteer study at the National Institute of Allergy and Infectious Diseases suggest that a modification of the fluorescent antibody technique is specific and provides a sensitive means of titrating antibody produced in malarial infections, it was reported to the Southern Society for Clinical Research meeting in New Orleans.

NIAID investigators applied the technique in blood tests of nine normal human volunteers infected with plasmodium vivax and plasmodium cynomolgi malaria. Thus, they were able to demonstrate antibody approximately 3 weeks after inoculation, and found antibody still detectable 325 days after inoculation.

In this modification of the fluorescent antibody technique, the antibody-containing blood serum of a malaria suspect is applied to a blood smear containing malaria parasites. If malaria antibody is present in the patient's serum, it will react with the malaria parasite. This union of antibody and parasite is detected by then adding horse antihuman antibody labeled with a special fluorescent dye. Together these form a conjugated substance which glows a bright yellow color when stimulated by ultraviolet light.

Associated in the NIAID study are Dr. Sanford F. Kuvin, of the Laboratory of Clinical Investigation, Drs. John E. Tobie and Charles B. Evans, Laboratory of Immunology, and Drs. G. Robert Coatney and Peter G. Contacos, Laboratory of Parasite Chemotherapy.

CAPACITY OF SIMIAN MALARIA TO PRODUCE HUMAN INFECTION ENHANCED BY PASSAGE TO MAN

Once the parasite of monkey malaria has been passaged to man, its capacity to produce human infection is increased markedly. Evidence of this is presented in the American Journal of Tropical Medicine and Hygiene by Drs. G. R. Coatney, H. A. Elder, P. G. Contacos, and M. E. Getz of the Laboratory of Parasite Chemotherapy, National Institute of Allergy and Infectious Diseases, and Drs. R. Greenland, R. N. Rossan, and L. H. Schmidt of the Christ Hospital Institute of Medical Research, Cincinnati, Ohio. The Christ Hospital investigators received support from an NIAID research grant.

Since last year's discovery in the Laboratory of Parasite Chemotherapy that man can become infected with simian malaria, the transmissibility of these

malarias to humans is being studied intensively, as are clinical and parasitological features of induced infections, to assess the importance of the animal disease in worldwide malaria eradication.

Originally only 1 of 7 human volunteers gave evidence of infection when *Plasmodium cynomolgi bastianelli* was transmitted to man; only 1 of 11 volunteers in the present study became infected when the M strain (maintained in the laboratory since 1935) was the infecting malaria. In the first effort, patent infection appeared in 82 days; with the M strain in 17 to 19 days. The parasite could be transferred from man to monkey to man; man to man; could be induced by blood or by mosquitoes. After residence of the M strain in two human subjects, it was passaged to the monkey and then to the mosquito. Three of four human volunteers bitten by these mosquitoes became infected.

The scientists also investigated the possibility of an alteration in the disease-producing capacity in animals of the M strain of *P. cynomolgi* after its passage through humans. Blood specimens from human volunteers were subinoculated into normal rhesus monkeys at selected intervals. When disease was established, the numbers of parasites in the blood of these monkeys was compared with those in another simian group inoculated at approximately the same time from the stock M strain. Apart from differences in time of initial appearance of parasites in the blood, the patterns of all infections were remarkably similar. This suggested that transfer of the M strain from monkey to mosquito to man had not altered the capacity of this parasite to produce characteristic disease in the monkey.

Results of these studies strengthen the investigators' belief that the previous demonstration of the transmissibility of *P. C. bastianelli* from monkey to man is not an event that is limited to that particular strain. The likelihood that additional strains of *P. cynomolgi*, as well as other malaria species, may be infectious for man is a possibility which should not be discounted. The resolution of this aspect of the problem of transmission of malaria could be of great importance in worldwide malaria eradication.

AMODIAQUINE AND CHLOROQUINE FAIL TO SUPPRESS A SOUTH AMERICAN STRAIN OF MALARIA

Further study of chloroquine and amodiaquine, which last year were found ineffective as a cure for the Colombia, South American strain of *Plasmodium falciparum*, has produced evidence that these drugs are also ineffective in suppressing the infection. Dr. Martin D. Young of the Laboratory of Parasite Chemotherapy, National Institute of Allergy and Infectious Diseases, reports this result in Transactions of the Royal Society of Tropical Medicine and Hygiene.

Eight patients who had formerly had malaria were given either 300 milligrams of chloroquine or 400 milligrams of amodiaquine weekly (dosages which ordinarily suppress malaria when taken regularly), with one out of each group of four serving as a control. Parasites and fevers developed similarly in patients taking the drugs as well as in the controls who received no drug. Continuation of the weekly dosages appeared to have little effect upon the subsequent course of the malaria infections.

Other drugs such as paludrine and pyrimethamine were effective against this malaria, indicating no cross-resistance for the particular strain tested. Atabrine was effective in some cases, although relapses did occur.

In an area where malaria parasites have demonstrated resistance to chloroquine and amodiaquine, it appears that normal suppressive dosage will no longer protect against malaria. Since these drugs are widely used as suppressive agents in areas where malaria occurs, Dr. Young emphasizes the importance of recognizing the problem of resistance in strains of *P. falciparum*.

ANTIGENIC STRUCTURE OF INTRACELLULAR STAGES OF RODENT MALARIA DEMONSTRATED

Cell-free preparation of erythrocytic stages of *Plasmodium vinckei* fractionated. Number of separate antigenic factors observed. Each induces formation of precipitating antibody.

Drs. Dan Spira and Avivah Zuckerman, of the Hebrew University in Jerusalem, grantees of the National Institute of Allergy and Infectious Diseases, comment that antigenic analysis of bacteria has progressed rapidly in recent years but analysis of protozoan cells has only begun. Their study of *P. vinckei*, a rodent malaria strain 100 percent fatal to white mice, breaks new ground in that the

separate antigenic components of intracellular stages of parasitic blood protozoa have never, to their knowledge, been demonstrated.

Blood was collected from mice at peak infection. Luekocytes and erythrocytes were discarded, and a parasitic sediment infective to mice was extracted. Rabbit antisera yielded a series of precipitation arcs against the plasmodial extract when examined by immunoelectrophoresis.

Two groups of controls, one tested with normal rabbit serum, the other with washed mouse red cells or stromata, were uniformly negative, indicating that the precipitating factors developed in response to the plasmodial extract, and that the plasmodial preparation was uncontaminated with red cell components capable of producing precipitin in rabbits. The authors conclude, therefore, that erythrocytic forms of *P. vinckei* contain a series of distinct antigenic factors, each capable of eliciting the production of precipitating antibody in rabbits.

The results of the study appear in Science.

NEW MALARIA PARASITE, PLASMODIUM COATNEYI, NAMED FOR NIAID SCIENTIST

A recent finding during intensive studies of simian malaria by scientists of the National Institute of Allergy and Infectious Diseases Laboratory of Parasite Chemotherapy is a new species of malaria parasite which they have named *Plasmodium coatneyi* in honor of Dr. G. Robert Coatney, Chief of that Laboratory.

The scientists, working at a field laboratory in Kuala Lumpur, Federation of Malaya, have described the new parasite in detail in the American Journal of Tropical Medicine and Hygiene. Authors are Drs. D. E. Eyles, and McWilson Warren and Miss Elizabeth Guinn of NIAID, and Drs. A. A. Sandosham and R. H. Wharton and Mr. Y. L. Fong of the Institute for Medical Research, Kuala Lumpur.

One unique feature of the newly recognized parasite is that the type strain was isolated from the mosquito vector, *Anopheles hackeri*, rather than from the primate host. The investigators suggest that since the cycle of infectivity of *P. coatneyi* resembles that of *P. falciparum*, one of three important human malaria parasites, the former may be highly useful for study in the laboratory.

BACTERIAL DISEASES

USE OF NEOMYCIN IN SURGERY ASSOCIATED WITH INCREASE IN TYPE 54 STAPHYLOCOCCUS

For the past several years bacteriophage type 80/81 *Staphylococcus aureus* has been the single commonest strain causing infection in hospitalized patients, with strains not typable at routine test dilutions (RTD) accounting for about 25 percent of infections. At the Johns Hopkins Hospital a change was noted in 1960, when 70 percent of staphylococcal infections were caused by strains which could not be typed at RTD. When retested with concentrated bacteriophage (1000 x RTD) about 33 percent previously nontypable were identified as type 54.

Drs. L. S. Cohen, F. R. Fekety and L. E. Cluff, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, report their study of the change in ecology of hospital staphylococci in the New England Journal of Medicine. Partial support was provided by a grant from the National Institute of Allergy and Infectious Diseases.

A survey was made of the use of antibiotics during the period when type 54 was emerging as the strain most hazardous to hospital patients. Type 80/81 and type 54 differed most widely in their resistance to neomycin. Type 80/81 was almost completely sensitive, type 54 almost completely resistant. The investigators found that the emergence of type 54 could be correlated with an increase in use of neomycin in preoperative sterilization of the bowel. Although only half the patients infected by type 54 actually received neomycin, these may have been the source of the others' infection since type 54 was the single most common staphylococcus colonizing the noses of surgical patients.

During this study only 1 of 100 hospital personnel harbored type 54 nasally at a time when 5 of 100 personnel carried type 80/81. Type 80/81 continued as the commonest staphylococci in personnel, and no infections among hospital staff were attributed to type 54.

The investigators believe that increased use of neomycin for preoperative bowel preparation may have caused type 54 staphylococci to become virulent for surgical patients. In addition, the observations suggest that type 54 may be less able to colonize and may be a lesser threat to well adults than type 80/81.

CELL WALL GROWTH FOLLOWED DIRECTLY FOR FIRST TIME

In the past, information concerning cell wall synthesis during cell division has been obtained by indirect and retrospective methods. These methods have established that, in general, a thickening appears along an equatorial circumference of the dividing cell, growing toward the center, or centripetally, to form an annular, or ringlike, cross-wall. The mode of elongation of the peripheral wall of the cell is not subject to verification by indirect means, although some investigators, using darkfield and phase microscopy in addition, have claimed that cell wall growth occurs by a general insertion of new material throughout the wall.

Drs. Roger M. Cole and Jerome J. Hahn, of the National Institute of Allergy and Infectious Diseases' Laboratory of Infectious Diseases, have succeeded in labeling bacterial cell wall differentially with fluorescein, enabling them to distinguish portions of different relative age, and thus to observe growth directly. Their observations of the organism *S. pyogenes* appear in *Science*.

The results of this investigation suggest that cell wall synthesis in actively growing cultures of group A streptococci usually occurs simultaneously at at least two sites per coccus, the various sites representing stages of successive divisions.

In addition, their findings indicate that cell wall growth in *S. pyogenes* is not by general insertion of new material throughout the cell wall but begins at the equator of the coccus and then extends both centripetally and peripherally.

The authors caution that their findings and interpretations apply only to *S. pyogenes* adding, however, that the methods they describe should be widely applicable.

STAPHYLOCOCCAL COLONIZATION IN NURSERIES REDUCED BY EFFECTIVE WASHING

Grantees of the National Institute of Allergy and Infectious Diseases at the Yale-New Haven Medical Center report they virtually eliminated staphylococcal nasal colonization of newborn infants by following a carefully designed method of hexachlorophene washing. Their study, reported in the *New England Journal of Medicine*, was designed to challenge a similarly successful program of infant washing at Palo Alto-Stanford Hospital Center. The earlier study was also supported by NIAID.

The Yale research shows that 51 percent of 500 consecutive "unwashed" control infants were positive (30 percent nasal colonization and 42 percent umbilical colonization) as compared to only 3 percent of 965 consecutively "washed" infants (2 percent nasal colonization and 1 percent umbilical colonization). The authors, Drs. Louis Gluck and Harrison F. Wood, state that although previous experiments have indicated that hexachlorophene washing may prevent infant-to-infant transmission of the bacteria, other trials dispute the effectiveness of the various washing methods. They also note that "there has as yet been no clear definition or intensive investigation of the role of antisepsis in the nursery."

The Yale investigators suggest a new epidemiologic route by which nasal colonization of infants by staphylococci may occur. Staphylococci are introduced into the nursery by the many environmental factors described by previous investigators but, according to the authors, staphylococci "colonize the umbilical cord and skin of newborn infants first. They may then be borne into the nose chiefly by the infants own random hand movements."

The bacteria are then transmitted back into the hospital environment and to infant carriers who upon discharge carry the infection into the community. The Yale investigators interpretation of the marked effectiveness of their hexachlorophene washing technique is that it prevents the first step of skin and cord colonization.

METHOD DEvised TO INCREASE RESISTANCE OF MICE TO STAPHYLOCOCCUS

Grantees of the National Institute of Allergy and Infectious Diseases report that they have increased significantly the resistance of mice to experimental staphylococcal and other diseases by injecting them with an extract of an epidemic, 80-81 strain of staphylococcus. The work of the grantees, Dr. Alfred L. Florman and associates of Mount Sinai Hospital, New York City, and North Shore Hospital, Manhasset, N.Y., is reported in the *Proceedings of the Society for Experimental Biology and Medicine*.

A staphylococcal infection—which causes death in mice usually between 8 and 24 hours—was produced by challenging the mice with the epidemic strain. Only 32 percent of 115 control mice survived, as compared to 69 percent of 111 mice pretreated with an extract of the same organism 20 hours before challenge. The difference of 37 percent is highly significant.

However, since both the extract and challenge had been given by the intra-abdominal route, the possibility that this represented only peritoneal blockade had to be excluded. This was done by giving the challenge intracerebrally. In these experiments, only 24 percent of the 198 control mice survived as contrasted to 56 percent of 199 mice given the extract. This difference of 32 percent is also significant and indicates that the protective effect is not local but systemic.

Experiments were also carried out to show that the protective effect of the extract injections was unrelated to the size and age of the mice. In three experiments, infecting organisms other than the epidemic strain were used and results indicate that this enhancement of protection is nonspecific.

This mode of action of this staphylococcal extract is unknown. The investigators ruled out properdin involvement, stimulation of the reticuloendothelial system by the extract, and interference mechanism, or antibody protection.

Since the extract is relatively nontoxic, the investigators suggest that it offers interesting possibilities for further investigation. If it can be shown to work in other species, they say, it may prove to be a useful prophylactic agent—not only against staphylococcal infections, but against a variety of other bacterial diseases.

"STAPHYLOCOCCUS AUREUS" STRAINS RECOVERED FROM RETAIL MEAT

Many investigators have found that potentially virulent *Staphylococcus aureus* strains are widely distributed. These organisms have been shown to exist on almost every type of object and in almost all environments where man and certain types of animals are present. Such broad occurrence may be either a consequence of or a contributing factor in the spread of these strains in outbreaks of staphylococcal infections in man. Foods, particularly unfrozen meats, seem to have been overlooked as possible sources of dissemination of these organisms.

Dr. James M. Jay of Southern University, Baton Rouge, La., a grantee of the National Institute of Allergy and Infectious Diseases, conducted a study of 4 types of meat; hamburger, pork chops, beef liver, and round steak to determine the market meat's content of coagulase-positive *S. aureus* and to characterize the market staphylococci in order to ascertain their similarity to strains in human infections. The investigation is reported in the Journal of Food Science.

Fresh meat for the study was purchased over the counter at 28 retail grocery stores and meat markets selected at random in the Baton Rouge area. Meat from 21 of the stores yielded coagulase-positive staphylococci; 136 isolates were recovered, of which 97 were phage-typable, representing 32 phage strains. At least 21 of these 32 strains have been recovered from humans.

The hemolysin patterns of 70 percent of the isolates were similar to those of human strains of *S. aureus*. It was found, however, that all of the isolates were sensitive to penicillin, erythromycin, chloramphenicol, and Kanamycin, which is generally not the case with clinical isolates from humans.

It is somewhat difficult, the investigators say, to draw conclusions from the data as to the main source of *S. aureus* in market meat and the actual role, if any, of the meat in the spread of staphylococci among the population. Since evidence was found indicating human and nonhuman sources, the author suggests that involvement of both sources is likely, the human source being perhaps the lesser contributor.

PURIFIED STAPHYLOCOCCUS PROTEIN SHOWN TO HAVE SEVERAL TOXIC PROPERTIES

Citing Rene Rubos' emphasis that current studies on acquired immunity to staphylococcal infections are hampered by use of crude fractions, Surenda Kumar and associates, grantees of the National Institute of Allergy and Infectious Diseases at the University of Minnesota, have purified *Staphylococcus* alpha hemolysin protein by electrophoresis and have shown that it dissolves blood corpuscles, destroys skin tissue and is lethal in rabbits.

Their findings support the "unitarian theory" that these toxic activities reside in a single fraction—a theory some doubted, because previous demonstrations

employed crude fractions or were peripheral to the problem. The current report in *Journal of Experimental Medicine* describes the tests that demonstrated purity of the fraction. Also, rabbits immunized with purified alpha hemolysin from *Staphylococcus* produced detectable antibody only to this fraction.

NEW CHOLERA VACCINE SHOWS PROMISE IN FIRST PHASE OF TESTING

The first phase of human testing of a new type vaccine shown to offer protection against cholera in mice has been successfully completed and further serological tests in volunteers will be undertaken with the National Institute of Allergy and Infectious Diseases grant funds.

After extensive experimentation in animals, the new immunizing agent has been tried in a group of nine humans, including the two medical investigators who developed the vaccine and seven graduate students. None experienced any significant toxic reactions and all produced substantial amounts of anticholera immune substances in their blood serums, in the human trials supervised by Dr. Etta M. Macdonald.

The new vaccine was extracted from El Tor vibrio cultures during 3 years of research by Dr. Yoshikazu Watanabe of the Kitasato Institute of Tokyo and Dr. W. F. Verwey of the University of Texas.

This vibrio caused serious choleralike epidemics recently in Hong Kong, Pakistan, and Thailand. Last year an El Tor epidemic claimed more than 1,500 lives in the Philippines, which had been cholera-free for many years.

The new immunizing agent has been proven to protect animals against both El Tor infection and true cholera infection, the research scientists said.

Ordinary cholera vaccine which has been in use many years has had two major shortcomings: (1) it has been variable in its effect as an immunizing agent, and (2) it produces an undesirably high frequency of local and general toxic reactions.

So far the new immunizing agent has been directed against only one (Agawa) of the two major types of cholera organism, and the renewed NIH grant will also support research on extracting a corresponding immunizing substance from the second (Inaba) type of cholera organism. The El Tor vibrios causing choleralike infection also are of these two types.

Laboratory experiments have indicated the new agent is much stronger in its immunizing effect and less toxic than ordinary cholera vaccine. The initial trials in humans have borne this out, but the numbers of people involved have been limited. More extensive work must precede trials under field conditions.

ADJUSTMENT OF URINE pH MAY ENHANCE ANTIBACTERIAL ACTIVITY IN URINARY TRACT INFECTIONS

In resistant urinary tract infections, which usually involve obstruction, the replacement of bacterial strains sensitive to antibacterial agents by strains resistant to them complicates therapy. The difficulty in treating such infections, and the possibility of improved management through employment of antibacterial agents effective at specific pH ranges, led National Institute of Allergy and Infectious Diseases grantee Dr. Thomas W. Mou of Upstate Medical Center, State University of New York, to determine the urinary pH at which several of the most valuable antibacterial agents exert their maximal effect.

In the laboratory phase, findings were based on at least four different bacterial inocula and a minimum of three concentrations of antibiotic in a range therapeutically attainable in human beings. Short-term clinical studies of 30 patients also were made. Each completed periods of specific antibacterial therapy under both acid and alkaline conditions.

Staphylococcus aureus, *Streptococcus faecalis* and *Pseudomonas aeruginosa* were inhibited most at an acid pH by all agents studied except streptomycin which was generally more effective in alkali.

Dr. Mou's studies are reported in the *Journal of Urology*.

RICKETTSIAL DISEASES

NEW METHOD OF PURIFYING PATHOGENIC RICKETTSIA GIVES HIGH YIELD OF PURE ORGANISMS

Purifying large amounts of rickettsiae by differential, continuous flow centrifugation from molar salt solutions followed by ether treatment produces rickettsial material possessing protective qualities fully equal to conventional

rickettsial vaccines and in addition reduces the amount of undesirable contamination with egg white antigen.

The method was developed by Dr. Richard A. Ormsbee, Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases.

Human sensitivity to egg proteins is well established and is one of the factors which makes the purification of rickettsiae important. Also, studies of chemical composition and antigenic qualities of rickettsiae depend primarily upon the availability of very pure preparations. In addition to providing quite pure suspensions of the organism, this method is relatively easy and quick, and results in efficient production of large amounts of purified organisms. Tests to date indicate that the preparations are fully potent protective antigens in animals.

Dr. Ormsbee worked with four rickettsial strains which cause human disease: (*Coxiella burnetii* (Q fever), *Rickettsia prowzekii* (louse-borne typhus), *Rickettsia mooserii* (murine typhus), and *Rickettsia rickettsii* (Rocky Mountain spotted fever)). With the new method he achieved large yields of purified rickettsiae from infected yolk sacs of embryonated chicken eggs. In *C. burnetii* preparations particularly, the amount of detectable egg white antigen was reduced to very low levels.

Dr. Ormsbee believes that these features make it feasible to use the purified preparations as vaccines for humans and as standardized serologic reagents. He predicts that such vaccines will markedly reduce the incidence of untoward reactions in persons sensitive to egg-white or yolk-sac antigens.

The study of the nature and chemical composition of rickettsial antigens has been facilitated by the availability of large amounts of purified organisms. A phenomenon of note is described in the present paper. Two phases of *C. burnetii* organisms are recognized, phase I characterized by failure and phase II by ability to fix complement under certain specific conditions. During centrifugation, phase I Q fever organisms formed a white bottom layer with a sharply delimited upper boundary with a layer of brown contaminant above.

In contrast, phase II organisms formed a cream-colored bottom layer graded evenly into the brown overlay. This is clear evidence of a structural or chemical difference between organisms in the two phases, and is the first time a variation of this nature has been recognized.

The work is reported in the Journal of Immunology.

FUNGUS DISEASES

CASE OF MYCOTIC ENDOCARDITIS CURED BY TREATMENT WITH AMPHOTERICIN B

Cases of mycotic endocarditis are increasing and more effective therapy is needed. All previously reported cases have died after illnesses ranging from 5 to 31 months in duration. Successful intravenous treatment with amphotericin B of a patient with evidence of disseminated histoplasmosis, endocardial involvement and major arterial involvement is reported in the Archives of Internal Medicine. According to the investigators, Drs. Bennett M. Derby and Katherine Coolidge, Public Health Service postdoctoral fellows, National Institute of Allergy and Infectious Diseases, and David E. Rogers, of the Department of Medicine, Vanderbilt University, Nashville, Tenn., only 1 of 12 previously reported cases was treated with amphotericin B, given orally in what is now regarded as very small doses. Therapeutic levels, they note, cannot be obtained except by intravenous infusion.

The investigators point out that amphotericin B is far from an ideal agent. The need for prolonged intravenous administration, the systemic reactions, and the hazard of progressive renal impairment make maintenance of prolonged therapy extremely difficult. In the present case, daily amphotericin B infusions were discontinued after 87 days. The investigators report that the patient was in good condition 20 months after discontinuation of treatment; relapses usually occur within 6 months.

CANDIDA ENDOCARDITIS STUDIES UNDERSCORE NEED FOR BETTER THERAPY

Clinical and pathologic studies of candida endocarditis reported from the National Institute of Allergy and Infectious Diseases Laboratory of Clinical Investigation and the National Cancer Institute Pathologic Anatomy Branch comprise new material in a review of this disease in *American Journal of Medicine*. Principal author is Dr. Vincent T. Andriole, a U.S. Public Health Service research fellow presently at Yale University. Coauthors are Dr. Howard M. Kravetz, who was a clinical associate with Dr. Andriole at NIAID at the time of the study and is presently a clinical and research fellow, Allergy Unit, Massachusetts General Hospital; Dr. William C. Roberts, of NCI, and Dr. John P. Utz, of NIAID.

The authors point out that cases of mycotic endocarditis have increased. The development of many cases in the course of intensive antibiotic and steroid therapy and its occurrence as a complication of cardiac surgery provide evidence of this. They note that 15 of the 39 adequately documented, published cases of fungal endocarditis have involved species of candida. The present report adds six candida cases, which are presented in detail. Of these, five were observed at the Clinical Center, while one was observed at Walter Reed Army General Hospital. Identification of certain candida cultures was confirmed by Drs. Chester Emmons and Herbert Hasenclever, Medical Mycology Section, NIAID.

The principal clinical difference between candida endocarditis and bacterial endocarditis is the occurrence of large vessel embolism, a reflection of the large size of mycotic vegetations.

The investigators comment that treatment with intravenously administered amphotericin B was effective in reducing the colony count and clearing the bloodstream of candida organisms. However, the benefit was temporary and "the prognosis of candida endocarditis must presently be considered to be uniformly fatal." The use of large doses of amphotericin B for longer periods of uninterrupted therapy is suggested until more effective therapy is discovered.

An addendum to a portion of the review cites the first case in which the patient was ever cured (tricuspid valve removed by open heart surgery) reported by National Heart Institute grantee, Dr. Jerome H. Kay et al. in the *New England Journal of Medicine*.

CYSTIC FIBROSIS

PALPATION OF GLAND MAY AID DIAGNOSIS OF CYSTIC FIBROSIS

Proceeding from the observation that the submaxillary glands were enlarged in many cystic fibrosis patients, investigators supported by the National Institute of Allergy and Infectious Diseases and the National Cystic Fibrosis Research Foundation undertook a survey to determine the frequency of the condition in 106 cystic fibrosis children and 300 normal children. The researchers, Drs. Giulio Barbero and Maarten S. Sibinga, of the Children's Hospital of Philadelphia and the Department of Pediatrics, School of Medicine, University of Pennsylvania, found such enlargement in 92 percent of the cystic fibrosis children and 2 percent of the normal children.

Reporting in *Pediatrics*, they comment that this finding "* * * in the presence of clear signs of chronic recurrent respiratory disease and/or increase in bowel frequency with change in quantity and appearance of the stools, is certainly highly suggestive of cystic fibrosis. Such an observation would be supportive of the diagnosis of cystic fibrosis in much the same manner as the finding of prolapse of the rectum, which Shwachman has noted to be present in 20 percent of 205 patients with cystic fibrosis."

THURSDAY, MARCH 14, 1963.

NEUROLOGY AND BLINDNESS ACTIVITIES

WITNESSES

DR. RICHARD MASLAND, DIRECTOR, NATIONAL INSTITUTE OF
NEUROLOGICAL DISEASES AND BLINDNESSDR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF
HEALTHECKART WIFE, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF
NEUROLOGICAL DISEASES AND BLINDNESSB. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL
INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
11 Personnel compensation:			
Permanent positions.....	3,124	4,128	4,636
Positions other than permanent.....	159	284	287
Other personnel compensation.....	89	89	132
Total personnel compensation.....	3,373	4,500	5,055
12 Personnel benefits.....	298	420	478
21 Travel and transportation of persons.....	284	346	364
22 Transportation of things.....	48	41	45
23 Rent, communications, and utilities.....	180	155	163
24 Printing and reproduction.....	80	80	28
25 Other services.....	1,054	1,158	1,258
Payments to National Institutes of Health management fund.....	4,164	4,781	4,946
26 Supplies and materials.....	540	491	549
31 Equipment.....	881	519	553
41 Grants, subsidies, and contributions.....	50,360	65,044	74,973
Subtotal.....	61,162	77,436	88,411
Deduct quarters and subsistence charges.....	4	4	4
Total obligations.....	61,158	77,432	88,407

Personnel summary

	1962 actual	1963 estimate	1964 estimate
Total number of permanent positions.....	563	729	755
Full-time equivalent of other positions.....	26	44	43
Average number of all employees.....	517	660	715
Number of employees at end of year.....	615	798	903
Average GS grade.....	6.7	7.0	7.1
Average GS salary.....	\$6,133	\$6,637	\$6,679

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities:			
1. Grants:			
(a) Research.....	38,902	49,754	58,537
(b) Fellowships.....	1,231	2,023	2,054
(c) Training.....	10,227	13,267	14,382
Total, grants.....	50,360	65,044	74,973
2. Direct operations:			
(a) Research.....	6,240	6,749 ¹	7,193
(b) Collaborative studies.....	2,676	3,633	4,154
(c) Training activities.....	47	55	64
(d) Review and approval of grants.....	1,141	1,517	1,664
(e) Program direction.....	345	434	359
Total, direct operations.....	10,449	12,388	13,434
Total program costs, funded ¹	60,809	77,432	88,407
Change in selected resources ²	349		
Total obligations.....	61,158	77,432	88,407
Financing:			
Comparative transfers to other accounts.....	1,828	4,299	
Unobligated balance lapsing.....	7,776	1,729	
New obligational authority.....	70,762	83,460	88,407
New obligational authority:			
Appropriation.....	70,812	83,506	88,407
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353 and 76 Stat. 728) (-).....	-50	-46	
Appropriation (adjusted).....	70,762	83,460	88,407

¹ Includes capital outlay as follows: 1962, \$564,000; 1963, \$519,000; 1964, \$553,000.² Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1961, \$287,000 (1962 adjustments, \$717,000); 1962, \$1,353,000; 1963, \$1,353,000; 1964, \$1,353,000.

GENERAL STATEMENT

Mr. FOGARTY. The committee will come to order.

We have with us today Dr. Masland, Director of the Neurology and Blindness Institute. We will put your complete statement in the record.

(The statement follows:)

Mr. Chairman and members of the committee, it is a pleasure to appear before this committee to review with you the research and training developments of the past year directed toward the prevention and cure of neurological and sensory disorders.

Significant advances have been made in the Nation's neurological and sensory research effort during the Institute's 11 years. To a large extent, this has been possible because of Institute training support.

TRAINING

The training grant program of the Institute has begun to make notable contributions toward meeting research manpower needs in the areas of neurological disorders, as well as disorders of vision, hearing, equilibrium, and communication. Institute-supported training centers are in operation for scientists wishing postdoctoral training in the clinical and preclinical research disciplines. Additional centers are urgently needed and plans are in preparation for their establishment.

Important development in the Institute's training program have taken place this year. These include the establishment of support for training at the predoctoral and advanced postdoctoral levels, and the initiation of new or improved training programs in neurology, ophthalmology, and otolaryngology at medical

institutions where the need exists. The Institute also has broadened the intent of its program to support the training of medical personnel for careers in organized community health services and public health, as well as for careers in research and academic medicine.

The supply of well-trained professional personnel in these fields continues to be inadequate to meet the tremendous demand. Less than 1 percent of all certified physicians are neurologists. In private practice, there are 531 certified neurologists and in full-time teaching or research, 214. Clearly, the speciality of neurology is vastly undermanned when it is considered that at least 6 percent of the Nation's population suffers from neurological impairments, 12 percent of all deaths are caused by neurological disease, and 90 percent of all totally disabled dependents receiving social security benefits suffer from neurological disorders. In order to meet its goal of an accelerated output of well-trained neurologists, the Institute currently is focusing upon the training of teachers who can staff the necessary training programs.

Although the number of certified neurologists, neurosurgeons, ophthalmologists, and otolaryngologists engaged full time in teaching or research remains relatively small, the impact of Institute training programs is quite apparent. This year the number of full-time specialists in teaching and research in neurology increased from 139 to 214; in neurosurgery, from 58 to 90; in ophthalmology, from 64 to 98; and in otolaryngology, from 33 to 58. Thus, the Institute is beginning to meet the need for teaching personnel as a first step toward increasing the manpower needed in these crucial areas.

NEW PROGRAM APPROACHES TO RESEARCH

The increased availability of trained personnel is making it possible to organize a broad multidisciplinary attack against many unsolved problems whose causes until now have proven too complex to yield to investigation. Designed to facilitate broad attacks against specific disease problems, categorical clinical research centers and broad program projects are being developed at established institutions where outstanding research scientists with different backgrounds are available. These research staffs with basic and clinical skills can now more readily apply advanced knowledge to the study and treatment of patients with neurological and sensory disorders.

Currently, 15 categorical clinical research centers and broad program projects have been activated. These include three cerebrovascular research centers; two epilepsy centers; three neurological clinical research centers; five neurosensory centers focusing on disorders of vision, hearing, equilibrium, and speech; a center for broad basic study of cerebral and related systems, including fine structure modeling of neural networks; and a center for study of brain damage and defective brain development in children.

In addition to the organization of broad program projects and research centers designed to focus on specific disease problems, the Institute is employing the use of collaborative research in which the Institute, itself, participates in the development of programs to meet national needs; establishing planning groups of outstanding scientists responsible for maintaining a continuing overview of specific areas, and advising the Institute and the profession regarding program needs in given areas; and supporting conferences, symposia, and publications for rapid dissemination of research knowledge and highlighting of areas of research opportunity.

COLLABORATIVE RESEARCH

Through collaborative and field investigations, the Institute is increasing its role as an active partner in the development of programs directed against certain selected high-priority problems. The objective of these collaborative projects is to use the resources of the Institute as a means of mobilizing an intensive national research effort, or of highlighting areas of special need or unique opportunity.

A major program of this Institute is the large area of neurological disorders of infancy and childhood including disorders such as cerebral palsy, mental retardation, congenital malformations of the nervous system, and congenital blindness and deafness. As a group, these disorders afflict more than 6 million Americans, many of whom have been seriously disabled throughout their entire lives. In addition, another quarter of a million babies are born each year with these disabilities.

Central to the Institute's research relating to this area is its collaborative perinatal research project being carried out at the Institute and 15 medical centers. This study to determine relationships between factors affecting women during pregnancy and the neurological and sensory disorders of their offspring has already furnished a wealth of data far exceeding that thought possible. As of the end of last October, 30,500 pregnant women had been enrolled in the project and the initial goal of 50,000 pregnancies is expected to be reached by January 1, 1965. Some 400 articles have been published by project participants and by study-supported researchers. Facts, techniques, and methodologies developed are already finding a wide application and forming the basis of many new research studies.

The project has contributed to the advance of serological investigations of virus infections through the development and application of a microtechnique. Over 100 different viruses are now being serologically evaluated in pregnancy and almost all of these are currently being studied in complicated and normal cases.

Working with the collaborative project, this past year scientists at NIH have successfully isolated and cultivated the virus that causes rubella, an important source of congenital defects. This was an essential step toward the development of an immunization procedure, and scientists at NIH and in other laboratories are now evaluating an experimental vaccine to prevent the disease.

An upsurge of interest in placental physiology and pathology has been stimulated by the project and many research studies have been devoted to defining the importance of this organ in pregnancy outcome. Ancillary studies have also identified poorly recognized or previously undescribed placental anomalies and diseases.

Related biochemical studies have resulted in a better understanding of the biochemistry of asphyxiated newborns, coagulative disorders of the mother, enzymes in normal and abnormal conditions, mental retardation associated with amino-aciduria, and numerous other perinatal conditions.

Methods for evaluating the newborn and young child neurologically, physically, and psychologically have been generated by the requirements of the study. Films demonstrating detailed neurological examinations of the newborn and 1-year-old child have been produced and are receiving worldwide attention.

In addition to pursuing its main objectives, the project has had an impact on obstetrical and nursery patient care through its system of complete and meticulously systematic data collection. It has also had an influence on medical schools by engendering interdepartmental research, and on medical teaching by providing adequate case material and records. Perhaps the most important of the peripheral contributions of the study has been the interest it has fostered in greater collaboration among scientists in this field, not only in the United States but throughout the world. Cooperative perinatal research has been developed in Uruguay, Great Britain, Denmark, and Sweden, and there is a constant stream of inquiries and visits from American and foreign scientists for exchange of knowledge about these projects.

LABORATORY OF PERINATAL PHYSIOLOGY

A closely related collaborative project of the Institute is centered at the Laboratory of Perinatal Physiology in Puerto Rico. This unique primate facility is being used to investigate relationships between adverse factors present during the perinatal period and neurological disorders. More than 700 pregnancies, approximately equal numbers in the wild and caged colonies, have been observed. Six years of continual observation has revealed that there are far fewer pregnancy losses in free-ranging monkeys than occur in the caged colony.

Studies at this facility have provided invaluable information regarding oxygenation of the fetus, the effect of uterine contraction on the condition of the newborn, and the mechanism, pathology and therapy of neonatal asphyxia. In addition, animals from this colony have been used for the study of German measles and its role during pregnancy.

INFECTIOUS DISEASES OF THE NERVOUS SYSTEM

The Institute is directly involved in the development of a program for the study and detection of chronic and latent virus diseases of the central nervous system. To increase scientific awareness of this problem, in 1959 the Institute,

together with the World Federation of Neurology, supported a symposium dealing with encephalitides. Interest also has been heightened by discoveries of latent viruses capable of lingering in the nervous systems of animals over months or years and leading to slowly progressive neurological damage.

This year the Institute, in collaboration with the Patuxent Wildlife Research Center, initiated a new program specifically directed toward the investigation of such latent infections. Certain degenerative diseases of the nervous system are known to occur in wild animals and may be infectious. Specialized resources and, above all, the broad experience of the Fish and Wildlife Service, Department of the Interior, in gathering and handling wild animals, are critically important to these studies. Within the Patuxent Wildlife Research Center, efforts will be made to isolate viruses which may be causing such human diseases as multiple sclerosis, chronic epidemic encephalitis (a form of Parkinsonism), Kuru, amyotrophic lateral sclerosis, and certain forms of epilepsy of childhood.

Closely related to these studies are epidemiological investigations of these diseases in New Orleans and in a small facility on Guam.

AMYOTROPHIC LATERAL SCLEROSIS

The unusual frequency of amyotrophic lateral sclerosis, discovered in an epidemiological survey on Guam, is being further studied by the Institute. On that island, ALS is responsible for approximately 10 percent of the deaths among the adult Chamorro population. Originally it was thought that ALS was a genetically determined, inherited disease. Recent investigations, however, have found that it is also prevalent among the Carolinian population in this same area—a group not genetically related. Additional isolates of ALS have been discovered on the Kii Peninsula in Japan and more recently in an isolated region of New Guinea. It is conceivable that each of these represents an unusual genetic focus, but it is more likely that some environmental factor, common to Western Pacific islands, is responsible.

PARKINSONISM

In the study of amyotrophic lateral sclerosis on Guam, a relationship has been demonstrated between this disorder and a form of Parkinsonism with dementia. This unusual combination offers further clues regarding the causes of Parkinson's disease which is common in the United States. Drug therapy is making possible a modification of the symptoms of Parkinsonism. Also, surgical treatment, by manipulation of movement-regulating centers deep within the brain, offers considerable relief to sufferers from this disease.

DRUG EVALUATION

In addition to direct participation in research, the Institute increasingly is attempting to mobilize the efforts of groups of scientists for continual surveillance and direction of given fields, analysis of program needs, encouragement and development of research programs, and to serve as a medium for scientific communication.

Among such special groups is an Institute-sponsored committee on drug evaluation with separate panels on certain major disease categories. These panels, established subsequent to the conference on drug therapy in neurological diseases in 1959, have continued to develop improved techniques for evaluating drugs used to treat multiple sclerosis, Parkinsonism, headache, and neuromuscular disorders. This year, a pilot project for the evaluation of therapy in myasthenia gravis was launched.

Simultaneously, the roles and effects of drugs and teratogenic agents are being reassessed through the Institute's collaborative perinatal project and another perinatal project at the Kaiser Foundation Research Institute in California. Preliminary evidence from a large number of cases indicates that the average pregnant woman takes at least four different drugs during pregnancy. Controlled clinical trials with agents commonly used in pregnancy are already underway.

The development of each of these programs for evaluation of therapy requires the establishment of a central focus and coordination in data analysis. To date the Institute has attempted to develop these through its central office in Bethesda. To serve adequately the national need, however, each such focus should include not only the conduct of field trials, but also responsibility for maintaining a complete overview of the field, and an information center through which the profes-

sion can be rapidly advised regarding available drugs, their efficacy and the reported side effects. The Institute has under consideration a plan whereby the responsibility for such broad activities would be delegated to regional university-based disease study centers.

CEREBROVASCULAR DISEASES

For the past 4 years the Institute has been supporting a cooperative study of surgical therapy of aneurysms. The first years of this investigation were concerned with the development of methodology. Seventeen laboratories are now moving ahead with a program to evaluate various surgical and medical methods to provide definitive data regarding the best techniques to treat each of several types of cerebrovascular disease. Studies thus far show that surgery may be a superior form of treatment for patients who have suffered rupture of an aneurysm of the middle cerebral artery.

In spite of advances in surgical techniques, a large proportion of cases of intracranial hemorrhage, especially those resulting from high blood pressure, are not amenable to surgery. A recent study of the treatment of 312 patients with hypotensive drugs indicates that drug therapy has a significant effect in improving the survival rates of such patients.

Improved diagnostic procedures are aiding both surgical and medical therapy of cerebrovascular disease significantly. Improved diagnostic techniques for cerebral hemorrhages have been developed in angiography, while radioactive dyes are being used in locating arterial narrowing. Also, radioactive tracers are providing important information regarding the dynamics of blood flow and the regulation of the cerebral circulation.

Because of the mutual interest of this Institute and the National Heart Institute in cerebrovascular disease, a joint subcommittee has been established to assure surveillance of this field. It has provided for a bibliography of cerebrovascular disease to keep investigators informed of current developments. It is also planning a fourth cerebrovascular conference in 1964 to discuss new research approaches in the areas of rheoencephalography, cerebral edema, controlled clinical trials, and cerebral blood flow.

On the basis of epidemiological patterns emerging from current studies, scientists are delving deeper into some of the suspicious factors relating to cerebrovascular disorders. Working through the auspices of the World Federation of Neurology, the Institute has developed three separate collaborative studies on the pathology of the disease. These include studies of the large vessels at the base of the brain; the severity of arteriosclerotic changes; and the structure of the wall of the blood vessel.

INTERNATIONAL RESEARCH

There is no national monopoly on creative research and medical contemplation. For this reason, the Institute has found it advisable to expand its program to utilize the best international resources which may be mutually beneficial in solving common neurological and sensory problems.

One of the most important international programs is the support of so-called paired grants. These grants are made to specific medical centers in this country to work cooperatively in a designated research area with an outstanding research center abroad. At the present time 10 paired grants are active or in the process of negotiation.

Indirectly, the Laboratory of Perinatal Physiology in Puerto Rico has given added impetus to international research cooperation. The unique research opportunities this facility affords have drawn the interest of many scientists from other countries, especially from Central and South America. Thus it is rapidly becoming an important research center of particular acclaim in this hemisphere.

An international collaborative study of blood groups and chromosomes was initiated in 1962. The project involves the participation of six laboratories in Sweden, Holland, France, Italy, England, and the United States. The ultimate goal of the studies is to provide additional knowledge for the mapping of certain genes on the chromosomes.

International cooperation also is enlisted in many ways in epidemiological investigations which help provide clues to causes of disorders.

MULTIPLE SCLEROSIS

Perhaps the most significant advance this year in multiple sclerosis research has been a further elucidation of the autoimmune or oversensitive reaction of the body to its own tissue. In the case of multiple sclerosis, the reaction is thought to be against the nerve sheath which is characteristically destroyed. An increasing number of studies have indicated that patients with MS have antibodies in their blood resembling those seen in experimental allergic encephalomyelitis in animals. While not identical with MS, this experimental disease shows striking similarities to it.

Scientists now have more accurate information regarding specific chemicals, especially the protein fractions of the brain, which are involved in this autoimmune process. They have found that the circulating lymphocytes or white blood cells are capable of carrying the antibodies which injure the nerve tissue. Since the thymus gland and spleen have been shown to regulate the production of lymphocytes, their possible influences in multiple sclerosis must now be determined.

Scientists are also attempting to find practical ways of preventing the autoimmune response. At this time treatments which are effective in preventing the condition in animals are too drastic to be applied to humans. These involve X-ray treatment, creating a deficiency of vitamin C, and pretreatment with some of the brain extracts which under other circumstances actually produce the disease.

One of the factors influencing the experimental disease is exposure to sunlight, a finding which offers a possible explanation of the low incidence of MS in the tropics.

It is still assumed that there must be some other disease process which is responsible for causing the autoimmune state. A likely possibility is some hidden virus infection. For this reason, as previously mentioned, the Institute is establishing a special program for investigation of hidden and latent infections of the nervous system including viral agents in MS.

EPILEPSY

Important new advances have been made in our knowledge of the basic mechanisms responsible for seizures. For a long time it has been known that irritant substances implanted under the surface of the brain can produce focal irritation with resultant epilepsy in animals. Recently similar results have been produced by partial isolation of the cortex from the deeper structures beneath it. These observations provide a clue to the mechanism through which accidental injury of the brain or disease may lead to a seizure state.

Also new information regarding the development of the epileptic state in childhood has evolved. In petit mal epilepsy, a strong genetic factor has been demonstrated which appears to depend upon certain characteristics of the nervous system present primarily between the ages of 7 to 14 years. At this period the highest frequency for petit mal seizures occurs.

Experimental and clinical investigations, coupled with basic investigations of the chemical changes observed in various seizure states, are leading to continued improvement of drug therapy. A wide variety of anticonvulsant agents is now available and each makes some slightly different contribution.

MUSCULAR DYSTROPHY

The study of muscular dystrophy continues to contribute to the establishment of a more accurate categorization of the disease. Careful histopathological and histochemical examinations have demonstrated at least three new varieties of this disorder in which the basic processes are different. It is assumed that in muscular dystrophy, as in most of the inborn errors of metabolism, some specific enzyme defect exists. The major emphasis of the Institute's current research program is on the study of the many enzyme systems responsible for the creation and maintenance of muscle structure and function. An enzyme, phosphorylase, essential to the maintenance of necessary energy-producing chemicals in the muscle, has been found to be reduced in several forms of muscular dystrophy.

There have been several approaches to muscular dystrophy therapy. Since there is rapid breakdown of muscle in patients with the disease, and only moderate restoration, scientists are attempting to foster muscle regeneration by administering hormones known to stimulate tissue protein buildup.

Efforts have been made to counteract disturbances of high energy sources with the administration of a nucleotide related to the energy cycle. Although favorable results seem to be produced temporarily, the long-range results have not supported earlier optimistic reports. These studies, however, are pointing toward the basic defect in the dystrophic muscle and are providing leads toward specific therapies.

MYASTHENIA GRAVIS

Several important advances have been made concerning the cause of myasthenia gravis. For many years it has been known that tumors of the thymus were unusually common in patients with myasthenia gravis, and removal of such tumors, in some instances, was believed to be followed by remission of the disease. Since recent studies show that the thymus gland plays an important role in the immunological functions of the body, the existence of autosensitization in patients with myasthenia gravis is suspected.

Because of the frequency of spontaneous remissions and fluctuations of severity, carefully controlled field trials are necessary to evaluate therapeutic agents. The Institute this year has organized a collaborative study of therapy in which the initial investigation is concerned with the use of ACTH in certain limited cases of myasthenia gravis. This drug, which has an important inhibiting effect on the immune responses of the body, is believed by some investigators to have a beneficial effect.

DISORDERS OF VISION

In recent years, evidence has accumulated which indicates that some drugs are causing eye disorders. The alarming occurrences of severe retinal degeneration, produced by the widely employed antimalarial drug, chloroquine, has led to intensive studies of the course and early identification of the disorder and an attempt to prevent it by accelerating the excretion of the drug.

Evidence has also been produced this past year to show that long-term or large doses of cortisone can produce cataracts and that glaucoma, too, may result from protracted, intensive therapy with corticosteroids.

In spite of these new problems, a number of advances have been made relating to visual disorders. In eye inflammations, scientists have found that the safety of steroid therapy may be increased by combining steroids with another drug, IDU (5-Iodo-2-Deoxyuridine), previously reported as a dramatic cure for herpes simplex keratitis. In treating certain types of uveitis, a new antibiotic, spiramycin, has proved successful when combined with the usual chemotherapy.

In studying the role of histoplasmosis as a cause of uveitis, the production of the disease in pigeons has proved to be a valuable new resource. The disease has been produced by injecting pigeons with the organism and then exposing them to a cold environment or to steroid treatment.

Diagnosis and control of glaucoma has been aided this year by research which shows a normal variation of the intraocular pressure throughout the day with the highest pressure early in the morning. A refinement in glaucoma management has come with techniques for the measurement of scleral rigidity and increased knowledge of the way it is affected by certain drugs, diurnal variations, and other conditions.

Painstaking research in chemistry, nutrition, and other areas is revealing vital facts about the mechanism by which the eye's lens becomes cloudy. Studies of cataract formation in diabetic rats were traced to an early concentration of two kinds of sugars, glucose and fructose. On the other hand, an enzyme, called NA-K activated ATPase, has been found to help maintain the transparency of the lens by regulating the sodium-potassium balance.

Diabetic retinopathy, a later complication of diabetes, is another important cause of blindness. Although there is increasing evidence that diabetic patients whose conditions are well controlled are the least susceptible to retinopathy, satisfactory treatment and prevention of the condition are still far from our grasp. Marked improvement has been obtained by removing the pituitary, but too little is known of the other consequences of such surgery to recommend its wide use.

A new surgical technique, developed by grantees, for injecting liquid silicone into the vitreous chamber of eyes with retina detachment has brought both functional and anatomical improvement in cases previously unresponsive to treatment.

The need for more information on the incidence and prevalence of blindness is being met by a cooperative Institute program which utilizes existing State

registers of blind persons. The Institute is helping the State agencies to collect reliable, uniform statistics which can be projected to reflect national occurrence.

HEARING DISORDERS

A recent survey of 2,500 children in special schools for the deaf revealed that in 33 percent, deafness was a result of illness in early life—usually meningitis. In 17 percent, prenatal and perinatal causes were responsible for deafness. Among these, kernicterus and maternal rubella were the most common factors. Partly as a result of Institute-supported investigations, neurological damage due to kernicterus is now largely preventable. At the present time scientists are experimenting with the production and evaluation of a vaccine for German measles.

As a result of recent medical advances, the potential ability to control deafness now far exceeds the present performance. Thus the Institute is placing heavy emphasis on the development of simple and reliable screening tests through which hearing loss may be detected early in the infant and the pre-school child. Such detection is essential to prevent progressive hearing loss and to insure rehabilitation or special early training for the child with irremediable hearing loss.

Institute-supported scientists have made significant contributions to refinements of surgical techniques for otosclerosis, a major type of deafness in adults. Because the ultimate aim is prevention rather than treatment, however, the Institute is concentrating on pathological, chemical, and metabolic studies in an effort to determine the essential causes.

In order to strengthen the attack on speech and hearing problems, the Institute has now developed two new research centers. In addition, the training program is providing for 150 research specialists in otolaryngology in 1962, and for 194 in 1963. This year the program was broadened to include training for basic scientists who desire to study for advanced degrees in this highly technical specialty.

NEUROLOGICAL DISORDERS OF CHILDHOOD AND ADOLESCENCE

In addition to the research contributions of the collaborative perinatal project and the Laboratory of Perinatal Physiology, continued advances have been made in understanding the processes underlying a number of the inborn errors of metabolism relating to mental retardation.

Grantees have been able to identify an additional amino acid in "maple syrup urine disease," a rare disorder of amino acid metabolism in infants. This finding may make it possible to reduce neurological damage from this disorder by feeding infants a special diet.

Another inborn error of metabolism is also associated with abnormalities of the amino acids. In this connection, cerebromacular degeneration and death are associated with disturbances of kidney function. Efforts are now being made to find methods for the control of the abnormality of body chemistry which underlies this degenerative process.

Although the discovery of the role of Rh incompatibility and the development of exchange transfusions has almost eliminated kernicterus as a cause of mental retardation and cerebral palsy, research relating to other forms of neonatal jaundice, especially that occurring in premature infants, continues. In a study related to the collaborative project, it has been shown that existing standards for determining bilirubin levels were not sufficiently reliable to be used as guides for exchange transfusion, and new standards have been established.

Continuing research emphasizes the role of neonatal asphyxia as an important factor in mental retardation. It has been shown that a lowering of body temperature under certain circumstances may increase the body's tolerance to asphyxia by reducing oxygen requirements. Part of the damage produced by asphyxia has been demonstrated to be a result of ionic changes with acidity. Neutralization of these effects appears to reduce significantly the secondary effects of asphyxia. Simultaneously, the pathological picture resulting from pure asphyxia has been examined. Damage of the extrapyramidal system and specific injury of the central auditory pathways were found to be especially prominent features.

An important retrospective study of the obstetrical background of cerebral palsy, completed this year, again highlighted the significance of prematurity as a cause of mental retardation and cerebral palsy. Of those children suffering from

spastic paraplegia, over half were premature. Twin pregnancy, mechanical birth trauma, and asphyxia were also important factors.

CONCLUSION

Highly important gains have been made in recent years in treating and preventing some of man's oldest afflictions. The pool of qualified scientists has been enlarged. Numerous well-equipped laboratories have been developed which will serve as a background for further progress in research.

Important as these gains are, they are only beginnings in the search for new knowledge that is urgently needed to diagnose, treat, and cure the millions of men, women, and children who are handicapped by disorders of the brain and nervous system. In addition to its research and training programs, the Institute hopes to find solutions to some of the unsolved problems through its broad project grants using a multidisciplinary approach, treatment evaluation programs, collaborative research, epidemiological studies, disease study centers, and international collaboration.

The request for 1964, Mr. Chairman, is \$88,407,000 which provides for increases in grants for about 243 additional research projects as well as increases in direct operations. It is distributed among program activities as follows:

Grants:

Research-----	\$58, 537, 000
Fellowships-----	2, 054, 000
Training-----	14, 382, 000

Subtotal, grants-----	74, 973, 000
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Direct operations:

Research-----	7, 193, 000
Collaborative studies-----	4, 154, 000
Training activities-----	64, 000
Review and approval of grants-----	1, 664, 000
Administration-----	359, 000

Subtotal, direct operations-----	13, 434, 000
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Total 1964 appropriation request-----	88, 407, 000
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Mr. FOGARTY. Go right ahead, Doctor.

Dr. MASLAND. Mr. Chairman and members of the committee, although serious manpower shortages continue to exist in several areas, neurological and sensory research advances have been more numerous recently because of the growing availability of trained investigators. This year, the Institute further extended its training programs in neurology, ophthalmology and otolaryngology; established programs in predoctoral and advanced postdoctoral training; and extended training to medical personnel preparing for careers in community health services.

The increasing number of research scientists has contributed to the launching of broadscale, multidisciplinary attacks against specific health problems whose causes, until now, have proven too complex to yield to independent investigation. Thus, 15 categorical clinical research centers and broad program projects have given new impetus to research in many disease categories.

The Institute has accelerated its research in other respects this year. For example, it initiated an intensive search for latent viral infections in a number of obscure disorders such as multiple sclerosis and chronic epidemic encephalitis (Parkinsonism); added to its broad drug therapy program a new project for the evaluation of therapy in myasthenia gravis; and expanded its program on evaluation of surgi-

cal therapy of aneurysms to include the management of other types of cerebrovascular diseases.

The Institute's support of detailed analyses of the process of vision, and the many factors causing impaired vision, offer exciting new possibilities for prevention of blindness and ultimate restoration of sight. Last year's discovery of a treatment for a common infection of the cornea has now been combined with existing therapeutic measures for more effective prevention and therapy of other infections of the eye.

An important development during the past year has been the survey and recommendations of the panel on mental retardation appointed by the President. This Institute has financed and played an integral role in the work of the panel whose recommendations are designed to improve prevention and management of mental retardation. The national implementation of many of these recommendations will be greatly enhanced by the foundations which already have been developed by this Institute, with the support and direction of Congress, during the past 6 to 10 years.

These new programs, combined with a large number of independent investigations, several cooperative studies, and paired grants, are providing encouraging advances in the challenging attack against neurological and sensory disorders.

INCREASE REQUESTED FOR 1964

In conclusion, Mr. Chairman, the request for the National Institute of Neurological Diseases and Blindness for 1964 is \$88,407,000 as compared with the \$77,432,000 available in 1963. These funds will provide a net increase of \$8,783,000 in research grants; \$31,000 in fellowships; \$1,115,000 in training grants; \$444,000 in direct research; \$521,000 in collaborative studies; \$9,000 in direct training activities; and \$147,000 in review and approval of grants.

Mr. FOGARTY. Thank you, Doctor.

The 1963 appropriation, adjusted for comparability, is \$79,161,000 and the 1964 request is \$88,407,000, an increase of \$9,246,000.

However, there is a reserve against 1963 funds amounting to \$1,729,000 so the effective increase in 1964 is \$10,975,000—that is unless a reserve is applied after the appropriation is made.

How much of the reserve is forced savings?

Mr. KELLY. \$314,000.

Mr. FOGARTY. What accounts for the remainder?

Dr. MASLAND. \$915,000 in research grants; \$500,000 in training; and \$314,000 in direct research.

TRAINING PROGRAMS

Mr. FOGARTY. Last year, in its report, the committee stated that it was convinced that the overall training program should be carefully strengthened. What have you done in this regard?

Dr. MASLAND. During the past year we have experienced approximately a 20-percent increase in size of this program.

Forty-eight new grants have been initiated.

Mr. FOGARTY. Is this training now?

Dr. MASLAND. Yes; training. Forty-eight new grants have been initiated in addition to those related to the special fellowships.

In addition, two very important new programs have been started, although the impact of these cannot yet be measured. The first of these is an extension of the objectives of the graduate training program to include the training of scientists for community service activities as well as for research.

The other special activity has been in the general field of speech and hearing. Here we have initiated programs which will train Ph. D. candidates for speech pathology and for audiology.

These are areas of very serious shortage where the Ph. D.'s have a most important research contribution to make. In order to increase the availability of these specialized personnel, we are broadening our training program in this area to provide for the training of Ph. D. candidates as well as for advanced training for those who have completed the Ph. D. degree.

POSSIBLE USE OF FUNDS IN RESERVE

Mr. FOGARTY. Why couldn't you have used some of the money in reserve for training in 1963?

Dr. MASLAND. Mr. Fogarty, there are a number of reasons why there remain unspent balances in training funds this year when at the same time there are unquestioned shortages of personnel in these areas.

A very important reason is the relatively short period of time which has been available for programing in this area between the apportionment date and the time when applications were to be reviewed for this fiscal year.

In the second place, the programs not only have been held back for several years, but also we continue to be handicapped by staffing problems. When one is involved in initiating new programs it requires extensive staff work to contact the people in the field, and carefully evaluate proposals. The serious problems of staffing, which I indicated to this committee last year, have been only partly offset by the pay increase voted last year by the Congress. The pay increase has improved the situation, but its impact has not been felt until recently.

QUALITY STANDARDS

I would like to emphasize that, in keeping with what I know are the desires of this committee, we have insisted on a very high standard of quality within these training programs. It is our principle not to sacrifice this objective. Therefore, while we are returning funds to the Treasury this year, I would like to point out that we have disapproved almost \$2 million worth of applications simply because they did not meet the standards that we felt were suitable for training.

Another related factor, which considerably delays the process of starting new grants in these fields is the Institute's insistence on project site visits for every prospective training grant. We do not award any training grant, whether new or a continuation, without visiting the institution to be certain that the environment is suitable for this activity. These project site visits are quite time consuming.

Until recently, our training activity has been limited entirely to research training at the graduate level. For example, in the field of neurology, which is one of our areas of most critical need, there are at the present time only 53 universities which have the personnel and resources to provide training at this level. We have insisted that the man who is getting his advanced research training must have a very broad program of basic science in addition to his clinical training. He must have for example, neuropathology, a certain amount of chemistry, and a certain amount of research experience. It requires a strong institution to provide such a training environment.

In 31 other medical schools, which do not have this potential at the present time, there are very weak neurology programs. Furthermore, at least another 15 medical schools appear to have no definable program for neurology in their organizational structure.

One of the things we are moving forward with now is a new program to strengthen and develop centers for neurological training in those 31 institutions.

RESULTS OF INCREASED APPROPRIATIONS

Mr. FOGARTY. Since 1954, the appropriations by Congress have been more than the request every year.

Dr. MASLAND. Right.

Mr. FOGARTY. Congress voted a substantial increase last year. I was just wondering how that affected your programs in 1963.

Dr. MASLAND. We had approximately a \$2 million increase in actual grants in training last year, from a level of \$10 million a year before. So it was about a 20-percent increase. The number of trainees increased from about a thousand to 1,200—the number of grants increased from 184 to 232. The impact of this program is now beginning to be felt in terms of mature scientists entering into full-time careers of teaching and research.

Within the past year, there has been a very impressive development. According to the best figures that we have, the number of neurologists in full-time teaching and research has increased from 139 up to 241 in 1 year.

In neurosurgery, from 58 to 93; in ophthalmology, from 64 to 105; and in otolaryngology, from 33 to 66. This doubled in 1 year. These are the key people for our research and training programs.

UNDERGRADUATE PROGRAMS

Mr. FOGARTY. What about the undergraduate programs in the medical schools?

Dr. MASLAND. This is one of the key problems that we are attempting to work out.

Mr. FOGARTY. This has been a problem ever since the Institute was established.

Dr. MASLAND. That is right. As I mentioned earlier, there are 31 medical schools that have no graduate programs. These are institutions which could be important to our program from several points of view. Obviously there are good people going through these medical

schools, a number of whom would be available for training in these shortage areas. But the medical student who is not exposed to a scientific discipline in the course of his undergraduate training has no appreciation of its potential and opportunity and he is not very likely to select this as his specialty.

Thus our failure to develop a focal point for specialty training in these three disciplines—neurology, ophthalmology, and otolaryngology, in medical schools, is handicapping us in two ways. First, it means that a lot of people who might ordinarily go into these fields are not even aware of their potential. Second, those who are interested do not have the essential basic training that is required for them to go into graduate education. We must therefore find a mechanism for establishing a focal point for these specialty areas in each of the medical schools.

Mr. FOGARTY. What progress are you making?

Dr. MASLAND. One proposal has been that these be handled as developmental grants. Such grants might be made available to an institution—after careful negotiation to be certain that they are in a position to develop a research oriented program—in order for them to recruit capable people to direct a future training program.

Mr. FOGARTY. Are you running into the same trouble the National Mental Health Institute had years ago?

Dr. MASLAND. Very much so. One of the key problems is that the specialty of neurology is one which deals with handicapped persons many of whom are hospitalized in State institutions for mentally retarded and in psychiatric hospitals, which have a great many neurological patients. The specialty of neurology has a large component of serious incapacitating diseases. Often, this is not a particularly lucrative type of practice.

Training for neurology is a very long and difficult period. The monetary reward for private practice is not great and those who come into neurology are usually dedicated people. This is an area of national need and I am very pleased that in the last few years we are getting very good people.

Mr. FOGARTY. Most neurologists I know are doing pretty well in private practice.

Dr. MASLAND. Yes; many of them are.

SHORTAGE OF NEUROLOGISTS

Mr. FOGARTY. There are so few of them; that is why they are so busy.

Dr. MASLAND. I have the figures on manpower in these specialties which you might like to see.

Mr. FOGARTY. Put them in the record.

(The information follows:)

Status of manpower in clinical neurology and related sciences

	Neurology	Neuro-surgery	Ophthalmology	Otolaryngology	Psychiatry	Internal medicine
Practitioners.....	586	1,045	6,259	4,511	7,506	22,967
Percent.....	44	67	86	88	55	72
In training.....	375	373	817	431	2,732	5,449
Percent.....	28	24	11	8	20	17
Full-time hospital and administration.....	131	52	86	85	2,551	1,228
Percent.....	10	3	1	2	19	4
Full-time teaching and research.....	241	93	105	66	752	1,897
Percent.....	18	6	2	1	5	6
Preventive medicine.....	6	0	12	12	181	268
Percent.....	0	0	0	0	1	1
Total ¹	1,339	1,563	7,279	5,105	13,728	31,843
Percent of all physicians in this specialty.....	0.5	0.6	3	2	6	13
Total physicians.....						244,163
Approximate ratio, physicians to population.....	1/156,000	1/123,000	1/25,700	1/35,400		
Recommended ratio ²	1/67,000	1/100,000	1/20,000	1/34,000		

¹ Reference: "AMA Directory," vol. 16, supp. No. 1, Feb. 4, 1963.

² Recommendation of extramural training survey of NINDB, Dec. 23, 1961.

Dr. SHANNON. Can I comment on this point?

Dr. Masland has found it difficult to give totally informative answers. What he did not say is that he made a proposal to NIH, that is my office, and we discussed it with the Surgeon General's office for authority to initiate a totally new program of undergraduate training grants.

At the time the program was suggested, we had a comparable request from some of the other institutes and a request for the expansion of the teaching grants in heart, cancer, and mental health.

It was my judgment at that time that they had not made a sufficiently strong case in the special needs of neurology to embark on another teaching grant program and that if we agreed to support neurology, then we more or less would have to provide similar support for other institutes as well.

In the aggregate we were taking a large step forward in the field of aid to medical education. I think that if we have a resubmission of Dr. Masland's request together with more operational details as to how to go forward, we would make a favorable recommendation to the Surgeon General's office.

Mr. FOGARTY. Neurology is the lowest on the table you placed in the record.

Dr. MASLAND. An interesting thing in the field of neurology is this. You see there are a total of 1,300 neurologists—375 of them are listed as being in training—that leaves less than a thousand.

Half of those men, or about 44 percent, are practitioners. An unusually high percentage of neurologists are in full-time teaching and research.

In the whole country there are only 586 people who are practicing neurologists. These are not all certified. The best figure we have for the number of qualified neurologists is still only about 800 or 900.

Mr. LAIRD. Have you a list of those with you, Doctor?

Dr. MASLAND. No, I do not. Not of the individual people. I have a list of the membership of the Academy of Neurology. There are about 800. There are five States that still do not have a certified neurologist. This will be decreased to four this summer when a neurologist goes to Maine.

Mr. FOGARTY. For the summer?

Dr. MASLAND. He is going to stay.

Recently I have had some very interesting contacts with people in Philadelphia. We have been working closely with the Bureau of State Services, Division of Chronic Diseases, in trying to find ways to meet uncovered areas.

There is an area near Wilkes-Barre with a quarter of a million people with no neurologist in the area at all. It includes a VA hospital, and three or four other hospitals. The proposal was for a consultant from one of our training programs in Philadelphia to go 120 miles to Wilkes-Barre once a week as a consultant for that community.

It was felt that this would be better than nothing. However, when this man was approached, he said he was so swamped with responsibilities in Philadelphia that he did not see how he could assume any additional load.

SHORTAGE IN NEUROSURGERY

Mr. FOGARTY. The number in neurosurgery is about as low as neurology.

Dr. MASLAND. It is about the same. In terms of total numbers, the neurosurgeons feel that their situation is not as critical.

The major need in neurosurgery is for more people in teaching and research. In this field, the ratio of physicians to population is only slightly below the recommended ratio.

Mr. FOGARTY. Yes. I see that.

Dr. MASLAND. What we are trying to do in neurosurgery is to introduce more research training into this group. The same is true in ophthalmology and otolaryngology. Although there are shortages in terms of total numbers, our major weaknesses there have to do with research orientation and academic training. You see what a very small proportion of those men are in research. Only 1 percent of the otolaryngologists are in the role of teaching and research as compared to the 18 percent in neurology. The problems are quite different in these several areas.

Mr. FOGARTY. In neurology you are way down when you compare the recommended ratio to the approximate ratio of physicians to population.

Dr. MASLAND. There are only two States and the District of Columbia that have a ratio of 1 to 67,000. These are States that have training programs and the trainees are listed as neurologists.

Mr. LAIRD. I come from a small town in Wisconsin, Marshfield. We only have a population of 15,000, but we have people in both these fields in Marshfield. They are at the Marshfield Clinic.

Dr. SHANNON. They probably draw from outside, too.

Dr. MASLAND. You also have a very important training program at the university, one of those we are supporting.

RESEARCH IN HEARING DISORDERS

Mr. FOGARTY. What are you doing on research in hearing disorders, Doctor?

Dr. MASLAND. Mr. Chairman, this is one of the most rapidly developing parts of our program.

Our increases in this field have been greater—

Mr. FOGARTY. Both speech and hearing?

Dr. MASLAND. That is right. The developments are in several areas.

There have been very impressive surgical advances, particularly for people in the older age group, and the job of the surgeon has been completely altered. Before the time of antibiotics, the otolaryngologists spent most of their time on the infections in the ear and mastoid.

Now, the advances of medicine have pretty much put him out of that business.

RECONSTRUCTIVE SURGERY FOR OTOSCLEROSIS

You rarely have to operate on a mastoid any more. Instead, the otologist is addressing himself more to reconstructive surgery and, particularly, the surgery for otosclerosis.

This is one of the most common causes of deafness in the older age groups. It is a condition which results from thickening of the small bones which transmit the sound waves from the eardrum to the sensory organ of the internal ear.

For reasons which are poorly understood, but at present under investigation, in some individuals those bones become thickened and encased with a sheet that prevents them from vibrating.

The important recent discovery is a technique whereby this bone can be removed and replaced with a piece of plastic or a little piece of wire. In approximately 90 percent of the people who are operated on with this procedure, effective hearing is restored.

In fact, in almost 80 percent, normal hearing is restored. The chief complaint of the people who have this operation is that everything is too noisy. They are so accustomed to living in silence that at first it is quite a shock.

This has been a very dramatic development.

On the other end of the spectrum—

Mr. FOGARTY. How was this developed?

Dr. MASLAND. This is one of those things that was an evolution to which a number of people contributed.

Mr. FOGARTY. Did you contribute? Did your Institute contribute?

Dr. MASLAND. We contributed to the refinement of the technique.

The person who developed one of the most effective techniques is Dr. Shea from Memphis, Tenn.

There have been refinements of this technique and improvements which have been supported by the Institute.

One of the underlying things which has made this possible is the development of antibiotics.

Until that was done it was not safe to operate in these delicate parts of the ear because they became infected and were destroyed.

Now you can prevent the secondary infection with antibiotics.

DEVELOPMENT OF ANTIBIOTICS

Mr. FOGARTY. If it was not for antibiotics we would not have Salk vaccine, would we?

Dr. MASLAND. Probably not.

Mr. FOGARTY. Or would you have a vaccine for measles?

Dr. SHANNON. We would not have many of the virus advances.

The technique of tissue culture is basically responsible for the bulk of modern day virology and the use of tissue culture is due to the availability of wide spectrum antibiotics.

Mr. FOGARTY. In the area of antibiotics, it goes back to what?

Dr. MASLAND. Just before the war, 1942.

Mr. FOGARTY. Were they mostly developed in the pharmaceutical industry?

Dr. SHANNON. Penicillin was the first really important one and was developed primarily through the efforts of the university workers. They had some pharmaceutical support.

Mr. FOGARTY. The development of penicillin was supported by the Government, too?

Dr. SHANNON. Well, there is some misconception about that, Mr. Fogarty.

What the Government supported very extensively during World War II was the attempt to synthesize penicillin.

The basic development relative to separation and fermentation was an exclusive industrial development.

Mr. FOGARTY. I guess what I was thinking of is that because of the war a great deal of Federal funds were spent in this area to perfect it and get into production.

Dr. SHANNON. Well, again, I think we have to credit industry for the primary capital used in production.

The main thing that made this possible was the amortization of capital facilities that permitted them to build very large scale pilot plants and production plans.

This was the big Government contribution.

Picking up after World War II in streptomycin and broad spectrum antibiotics, I think this again was largely, if not totally, industrial.

Mr. FOGARTY. I remember the development of streptomycin. It was discovered the year I came to this committee. To get streptomycin you had to go through about 30 different processes and as a result, the first year there was not enough for some of the TB hospitals to do research with.

Then the committee appropriated \$2 or \$3 million over the budget that year to help industry to find the way of producing synthetic streptomycin.

Dr. SHANNON. I know this very well, because I was in industry at the time. These funds were used to purchase a very expensive quantity for clinical trials. These clinical trials could then be centralized so that a very small amount of streptomycin could go a long way to provide new knowledge.

This was the great contribution of this committee. Again, over the 3-year period that I was with Squibb, I would say that more than half of my total research budget had to do with process research on fermentation and separation of streptomycin. The same thing was going on at Merck and the other streptomycin producing firms.

So that industry, while it reaped a very rich reward, really put a very large amount of money at risk in the early days to bring this into being.

Mr. FOGARTY. But the industry has really profited greatly since the war.

Is there anything else you wanted to say about speech and hearing research?

LANGUAGE DISORDERS IN CHILDHOOD

Dr. MASLAND. At the other end of the scale, there have been developments in problems of language disorders in childhood.

It used to be that a child was spoken of as being deaf and dumb and that was it.

Now, we are learning that a great variety of different disabilities may be responsible for failure to learn to speak. Obviously, if a child cannot hear, he will not learn to talk because he will have no sound to imitate.

A number of children who do not learn to talk are disabled by injury of the conduction pathways of the central nervous system through which the sound travels from the ear to the brain.

Mr. FOGARTY. You mean they are born deaf?

Dr. MASLAND. They may be born this way or it may be the result of injury. For example, two conditions of the neonatal period—*asphyxia* and *neonatal jaundice*—have a very harmful effect on the auditory pathways by which the sounds are transferred from the ear to the brain. This produces a different type of disability than occurs if the ear itself is involved. It is a more remediable one. In other instances, there are actually abnormalities or defects of brain, itself, which make the individual incapable of interpreting a sound. Such individuals may hear a sound but be unable to understand its significance.

One of the most important advances of recent years is the development of methods for distinguishing with accuracy which of these mechanisms is involved. This is most important because the remedial or training procedure may be different in these several instances. Now we are developing training techniques which greatly improve our ability to deal with these children.

COLLABORATIVE RESEARCH PROJECT

We are attacking this from several points of view. We are utilizing the collaborative project very actively in this area.

Within this project we will have, as you know, some 40,000 children on whom we have a complete background history. Each of these children—

Mr. FOGARTY. You hope to have 50,000?

Dr. MASLAND. 50,000 mothers but, for a number of reasons, only 40,000 children who will be followed in detail.

Mr. FOGARTY. Well, this 40,000, have you reached that yet?

STUDY OF CHILDREN'S HEARING

Dr. MASLAND. We will not reach that for another year or so. With in the study, each child has a hearing and language development examination at the crucial stages.

A child ought to be speaking when he is 3 years old. Everyone of these children will be examined quite carefully to determine whether he is speaking and if there are deviations in his hearing and speech. Because he will be reexamined when he is 7 years old, we will have gained a more definitive evaluation of his condition and be able better to evaluate the earlier tests.

This is most important for two reasons. Some of the diseases which cause deafness in childhood can be remedied—such as chronic otitis media, infection of the ear. If this is recognized early and treated, the child can be saved from becoming deaf. So an early examination of hearing is most important to prevention.

In the second place, if a child has special problems in language development, it is essential that these be corrected before he becomes of school age. Since the preschool period is the age during which the language process normally evolves, this is when the special training should be most effective. Therefore, we are working very hard toward the development of a good battery of screening tests for children in the preschool period. We are working with the Bureau of State Services toward the implementation of such a battery as quickly as it can be refined.

The collaborative project, itself, is serving a unique purpose in the refinement of the test method and test examination which will be useful for screening these handicapped individuals.

Mr. FOGARTY. I wrote you a letter asking you to reply to four or five questions because of a remark made by one of our friends in Boston, that this collaborative project would fall on its face if it were not for you and still might.

Do you think it is going along pretty well and that it is going to be a successful project?

Dr. MASLAND. I am very enthusiastic about the development of the project. When I reported to this committee last year I expressed some serious concerns regarding the staffing problems we were having. These have been significantly improved since last year, particularly by the recruitment of unusually capable men in the field of biostatistics. We now have extremely valuable data at hand which is ready to be analyzed.

Mr. FOGARTY. What year are we in now?

Mr. MASLAND. This is about the fourth year of the actual recruitment of cases.

I think this project is even more significant in view of the recommendations of the President's Panel. The President's Panel made some far-reaching recommendations for mental retardation. The project on which we have been working, and which was set up at the recommendation of this committee, is actually providing a very important base for the implementation of these recommendations.

SPECIAL MATERNAL CARE FOR HIGH-RISK WOMEN

For example, one of the first recommendations of the President's Panel was for special programs of maternal care for so-called high-risk populations. These are women whose conditions indicate a greater likelihood of presenting problems in pregnancy. Now, this is exactly the sort of thing that this study has determined.

Mr. FOGARTY. What do you mean by high-risk populations? You mean in the slum areas or something like that?

Dr. MASLAND. That is one, but within any group of pregnant women, from whatever social or economic level they come, there are certain women who are more likely to have problems during pregnancy.

Mr. FOGARTY. What types of women?

Dr. MASLAND. Let me point out first that our study is only in its early stages and the children we are studying are still quite young. Therefore, our concern so far is with problems of the newborn and those occurring during the first year of life of which a very important one is prematurity.

On subsequent examination, 9 percent of premature babies are found to be neurologically damaged. The prevention of prematurity, therefore, is most important in preventing neurological disability.

In terms of the women who are likely to have premature children, we know that if a woman has had several previous premature babies, there is a 30 percent chance that the next one will be premature.

We know also that if a woman has high blood pressure, a small heart, or smokes, she is more likely to have premature babies.

A very important recent discovery is the role of cystitis, an infection of the urinary tract. Within a group of women who were found to have an asymptomatic bladder tract infection, 25 percent subsequently had premature deliveries.

We have discovered that certain emotional characteristics of the pregnant woman also relate to pregnancy outcome. A very interesting correlation has recently developed between an anxiety index of the pregnant woman and abnormalities of the 8-month old child. There was a correlation established here, but the exact meaning is difficult to determine. This is the type of investigation, now in its early stages, which should tell us, by reason of correlations, that the woman with certain characteristics is a bad pregnancy risk and every medical precaution should be taken with her.

That is one of the things toward which we are working.

EARLY DIAGNOSIS OF NEUROLOGICAL HANDICAPS IN INFANTS

Now, another one of the recommendations of the President's Panel was for diagnostic centers for the early recognition of mentally retarded and neurologically handicapped children. This is a second thing toward which this study has been making important contributions in methodology. I have previously referred to the contribution of the study in the field of hearing.

Referring to another phase of the study, we have learned that the examination of the placenta can be an important indication that the baby is likely to have problems. If the placenta is stained, it means that the baby has had difficulty. We have learned to look for evidence

of infection in the placenta because if the placenta is infected, the baby is likely to be infected and probably needs antibiotics.

It has been discovered that if there is an absence of one of the arteries in the umbilical cord, it is very likely the baby has had a congenital vascular malformation and the heart should be examined with special care to search for congenital heart disease.

As a matter of fact, in one series of babies who died, it was discovered at autopsy that in 16 percent the cause of death could be determined only by examination of the placenta. Thus the placenta provides a crucial clue to pregnancy abnormalities.

Another problem we have concentrated on involves the bilirubin because of the importance of jaundice. In a series of jaundiced babies with a bilirubin level above a certain figure, over 20 percent were later found to be damaged. We have reduced that figure considerably by employing exchange transfusion techniques. Most babies born today would not have as unfavorable consequences of jaundice.

We have also concentrated very much on clinical examination. The neurological examination of a small infant is a very highly specialized and difficult undertaking. Therefore we have prepared a film showing how to examine a 1-year-old baby. There have been over 300 showings of the film to professional audiences and it has been cited by the American Medical Association. The AMA is constantly circulating many prints of it and has recommended that it be shown to every intern and resident as part of medical training programs. These are some of the contributions in methodology that this study is making.

RESEARCH HOSPITALS FOR OBSTETRICS AND PEDIATRICS

Another recommendation of the President's panel was for the establishment of research hospitals for obstetrics and pediatrics. In a certain sense, we have almost 15 research hospitals as a result of this study. For example, when I visited the Providence Lying-In Hospital several weeks ago, Dr. Brooks pointed out that this has been an outstanding hospital for many years.

This institution has maintained unusually high standards of patient care over a long period of time. It was not a research institution, however. Now, with its participation in the collaborative project including the resources that it has been necessary to build within that institution and with the stimulus the project provides, this institution is reaching a stage now where it could quite appropriately be considered a research hospital.

Mr. FOGARTY. It has one of the best reputations in the country I think.

Dr. MASLAND. It has had for a long time, yes.

Within this collaborative project, over a thousand professionals have gained experience in research in this field.

Mr. FOGARTY. What about the Ladd School? Did you visit there?

Dr. MASLAND. I visited the Ladd School and was tremendously interested and impressed with what that institution is doing.

Mr. FOGARTY. What did you think of the new hospital?

Dr. MASLAND. Very nice. The circular hospital was very interesting in plan. I think one of their major objectives now is to establish

a working relationship with the newly developing medical school at Brown University. Thus, increasingly, this will become a teaching and research center which I think will be helpful for the institution and the university as well as important to the development of science.

Mr. FOGARTY. I do not know whether they told you or not—they are trying to raise funds for an outdoor swimming pool.

Are there any Federal funds available for anything like that? It is recreation but it is a health project, too, is it not?

Dr. MASLAND. It certainly is. Like the gymnasium, it is part of an effective rehabilitation program for a group of handicapped individuals.

Mr. FOGARTY. Do you know of any programs?

Dr. MASLAND. I do not know of any unless it would be in vocational rehabilitation in connection with a broadening of their mandate for self care types of programs.

Mr. FOGARTY. Go ahead. I did not mean to interrupt you.

TRAINING ASPECTS OF COLLABORATIVE PROJECT

Dr. MASLAND. I was remarking on the tremendous impact that the collaborative project has had in the training and orientation of people who have been involved. We calculate that over a thousand men have actually been involved in this research. These include obstetricians, pediatricians, neurologists, and other specialists who have had their attention drawn to this important field of research and who have been stimulated through this project.

We calculate that between 3,000 and 4,000 medical students have been in touch with these programs, thus becoming acquainted with this research approach to the problems of maternity and the prenatal causes of neurological deficit.

The ancillary studies have been very productive. There are now over 400 published articles from studies which have been carried on by people in this collaborative program or by other investigators using data regarding the children who are being thoroughly studied in the project. These are articles in the scientific literature, published by the most qualified journals.

Mr. FOGARTY. I think this is a very good report.

It does not look to me like this is going to fail.

Dr. MASLAND. We feel that what we have been doing is creating a national resource. It has a tremendous potential for a contribution.

For example, within this project we can continually monitor the population. When the thalidomide episode first started in Germany, someone communicated right away with one of our collaborators. They asked whether we were having this sort of thing in the United States. In the course of 1 or 2 days we were able to review our data and assure ourselves that this was not happening in the United States. If it were to happen in the United States next year, I believe that the study would detect it.

DRUGS TAKEN DURING PREGNANCY

We have information on drugs taken during pregnancy and I must say it is rather appalling. There were only 3.4 percent of our women who had not taken some drug during pregnancy. Over 96 percent had taken some kind of drug.

Mr. FOGARTY. What did they take drugs for?

Dr. MASLAND. Twenty-six percent had penicillin, 10 percent have had sulfa, 13 percent had phenobarital, 50 percent had had aspirin. A lot of them had had tranquilizers of one sort or another. It seems to be popular to take medicine.

Mr. FOGARTY. People generally do not take them unless a doctor prescribes it; do they?

Dr. MASLAND. Penicillin would be prescribed by a physician.

Mr. FOGARTY. Phenobarbital would, too.

Dr. MASLAND. That is true.

Mr. FOGARTY. What was the second?

Dr. MASLAND. Ten percent had sulfa drugs.

Mr. FOGARTY. Would that not be prescribed?

Dr. MASLAND. That would be prescribed.

I am not saying these drugs are not indicated, because, for example, if these women had bladder infection, the proper use of drugs could be most important.

The important thing is, we need to know whether these drugs are completely safe during pregnancy.

Dr. SHANNON. Mr. Fogarty, the lesson to be drawn from this drug experience is that pregnancy is a very stressful period in a woman's life.

A great many things go wrong that disturb the normal, daily routine of her life, including infection and physiological upset. I am not surprised at this drug intake at all.

Mr. FOGARTY. You are not?

Dr. SHANNON. No, sir.

I have gone through, by fairly proximate control, three pregnancies on the part of my wife. I know some of the problems she faced, at least she told me.

Mr. DENTON. Do they not take medicine and shots to avoid nausea? Is that not a rather common practice?

Dr. MASLAND. We had quite a few who had such medicines.

Dr. SHANNON. It is a common occurrence. We think this is a normal event in a woman's life. It is. But it is a very stressful event and it is sufficiently stressful that it makes many women susceptible to a large number of independent happenings that require medical attention.

Mr. DENTON. Do the shots for nausea they give women during pregnancy; does that have a bad effect?

Dr. SHANNON. Many physicians prefer not to create the risk of making them more nauseous by using oral medicine. Under these circumstances, the medication will be given by injection.

Dr. MASLAND. We have a list of drugs for motion sickness, anti-nausea drugs and antihistamines administered during pregnancy. If you add up all the figures, 20 percent of the women took such drugs. I do not think this is exactly correct because some women may have

had two or three different drugs and, adding the percentages for each drug, may have distorted the picture.

There was a suspicion a month or so ago that one of these drugs might be responsible for congenital malformation. However, we checked this out with another one of our grantees and are quite certain that this is not the case in respect to this particular drug.

We are paralleling this part of the collaborative project that I have been describing with a project at the Kaiser Permanente Foundation which has a prepaid health program. One of the advantages of this is that within a prepaid health program, all of the medical care of the woman is provided by that institution and data are available regarding prescribed medication prior to pregnancy.

Almost 8,000 deliveries a year are being followed in that institution. We are in a position now to collect data and check out a drug rather quickly.

RELATIONSHIP OF EXCESSIVE SMOKING AND PREMATUREITY

Mr. FOGARTY. Are you as concerned as you were before about excessive smoking on the part of women who are pregnant?

Dr. MASLAND. The data continue to indicate that prematurity is more common in women who smoke. We still have not launched the controlled study of smoking within which we will attempt to induce women to stop smoking to see whether that makes a difference. We have not figured out yet whether to scare them or reward them. One of the first things we may have to do is run a study to find out which would be the best. But before we could do this, we had to develop a method for finding out whether they were or were not smoking.

We now have a urine test which will tell if a person has smoked within 2 days before the urine specimen is taken. We are about ready to move ahead with that project.

PRESIDENT'S PANEL ON MENTAL RETARDED

Mr. FOGARTY. On the subject of the President's Panel on Mental Retardation, we will put section I of the Panel's report in the record. This summarizes the problem, their findings and recommendations.

(The document referred to follows:)

SECTION I

The mentally retarded are children and adults who, as a result of inadequately developed intelligence, are significantly impaired in their ability to learn and to adapt to the demands of society. An estimated 3 percent of the population, or 5.4 million children and adults in the United States, are afflicted, some severely, most only mildly. Assuming this rate of prevalence, an estimated 126,000 babies born each year will be regarded as mentally retarded at some time in their lives.

SIGNIFICANCE OF THE PROBLEM

Mental retardation ranks as a major national health, social, and economic problem:

It afflicts twice as many individuals as blindness, polio, cerebral palsy, and rheumatic heart disease, combined. Only four significant disabling conditions—mental illness, cardiac disease, arthritis, and cancer—have a higher prevalence, but they tend to come late in life while mental retardation comes early.

About 400,000 of the persons affected are so retarded that they require constant care or supervision, or are severely limited in their ability to care for themselves and to engage in productive work; the remaining 5 million are individuals with mild disabilities.

Over 200,000 adults and children, largely from the severe and profound mentally retarded groups, are cared for in residential institutions, mostly at public expense. States and localities spend \$300 million a year in capital and operating expenses for their care. In addition, they spend perhaps \$250 million for special education, welfare, rehabilitation and other benefits and services for retarded individuals outside of public institutions. In the current fiscal year, the Federal Government will obligate an estimated \$164 million for the mentally retarded, about three-fourths for income maintenance payments and the rest for research, training and special services. Federal funds for this group have nearly doubled in 5 years.

The Nation is denied several billion dollars of economic output because of the underachievement, underproduction, and/or the complete incapability of the mentally retarded.

The untold human anguish and loss of happiness and well-being which result from mental retardation blight the future of millions of families in the United States. An estimated 15 to 20 million people live in families in which there is a mentally retarded individual. Economic costs cannot compare with the misery and frustration and realization that one's child will be incapable of living a normal life or fully contributing to the well-being of himself and to society in later life.

THE IMPACT OF MENTAL RETARDATION ON THE PUBLIC

Mental retardation does not respect station in life or geography. It may afflict the children of the rich or of the poor, in any part of the country. Yet there are extremely striking variations in its incidence by socioeconomic groups and by geographic areas which often mirror such differences. From the growing body of research information on mental retardation, the following points stand out:

The more severe cases of mental retardation are likely to be associated with organic defects. However, in mild retardation, which constitutes the great bulk of the cases, specific physical or neurological defects are usually not diagnosable with present biomedical techniques.

The occurrence of severely retarded children tends to be spread more evenly throughout the population regardless of the socioeconomic class of the family. The prevalence of children who are mildly retarded is heavily concentrated among the parents with poor education and low incomes.

Selective service statistics reveal an extremely wide variation geographically in the prevalence of mental retardation. During World War II, 716,000, or 4 percent, of the persons examined were rejected on grounds of "mental deficiency." The percentage rejected for this cause ranged from only one-half of 1 percent in some States to nearly 14 percent in others. Regional rejection rates ranged from 1 percent in the Far West to nearly 10 percent in the Southeast. Nationwide, 7 individuals were rejected for mental retardation for every 10 turned down for mental disease.

The selective service statistics also show a much heavier prevalence of mental retardation among nonwhites than in the rest of the population. Draft rejection rates because of mental deficiency were six times as high for nonwhites as they were for whites. Of the total rejections of 716,000 for mental deficiency, 325,000 were nonwhites. In both categories there were substantial regional variations in the rejection rates. Among the whites, the rejections in the Southwest were six times as high for this cause as in the Far West. Among nonwhites, rejections in the Southwest were four times as high as in the Northwest. However, in every region the rejection rate for nonwhites was at least three times as high as that for whites; but the highest regional rejection rates for whites exceeded the lowest regional rejection rates for nonwhites. Modern science has indicated that such variations are due to lack of opportunity rather than hereditary or mental endowment.

Data from a representative nationwide statistical sample on the basis of which the Stanford-Binet intelligence tests were standardized in 1937 confirm the geographic variations in intelligence. In addition, they highlight a significant variation in intelligence according to the socioeconomic level of the families. For example, children of fathers who were day laborers had a mean IQ of 93.6, while children of professional employed fathers had an average IQ of 116.2.

These tests also show an inverse relationship between degrees of economic and social well-being and the rated intelligence in the intermediate ranges of vocations.

Strikingly high concentrations of mental retardation in specific sections of metropolitan communities also point to a strong correlation between economic status and intellectual development. A 1952 study in Chicago, for instance, showed that 65 percent of the pupils in special classes for the retarded came from 11 slum-ridden areas out of the 75 areas comprising the metropolitan community. In these 11 communities, the rate of referral for mental retardation among school-age children ranged from 10 to 30 percent. However, children too severely mentally retarded for school were fairly evenly distributed throughout the entire city.

Prevalence of mental retardation tends to be heavily associated with lack of prenatal care, prematurity, and high infant death rates. Women who do not have prenatal care are approximately three times as likely to give birth to premature babies as women who receive adequate prenatal care, and very small premature babies are about 10 times more likely to be mentally retarded than are children of normal births. The study in Chicago showed that infant mortality rates in the slum areas during the 2d through the 12th month of life were three times the rates in the best socioeconomic areas. In the United States in 1960, the infant mortality rate averaged 26 per 1,000 live births, but the State with the poorest record had a rate of 41.6, twice the rate of 19.6 in the State with the best record.

THE NATURE, THE CAUSES, AND THE EFFECTS OF MENTAL RETARDATION

The term "mental retardation" is a simple designation for a group of complex phenomena stemming from many different causes, but one key common characteristic found in all cases is inadequately developed intelligence. Many synonyms for the term "mental retardation" have been used in the past and are still in use. They include amentia, feeble-mindedness, mental deficiency, mental subnormality, imbecility, and morosity.

Because mental retardation is a relative concept depending on the prevailing educational and cultural standards, there is no completely satisfactory measure for mental retardation. Current scientific usage favors groupings based on the intelligence quotient (IQ) and adaptive behavior of the person. Four groupings are commonly used—profound, severe, moderate, and mild. They range from the situation where evidence of human adaptation is almost totally absent to that where the degree of impairment is minimal and the difference from normality almost indistinct.

As designated under the four categories based on intelligence quotient, those individuals who are considered profoundly retarded (IQ usually below 20) and those designated as severely retarded (IQ from about 20 to 35) need constant care or supervision throughout their lives if they are to survive. In these groups are the anencephalics, human beings without cerebral cortexes, and the more seriously impaired Mongoloids. There are an estimated 60,000 to 90,000 persons, mostly children and adolescents, who are profoundly or severely retarded. It is estimated that 1 child out of every 1,000 born, or somewhat over 4,000 births a year, falls in these 2 groups.

The moderately retarded persons (IQ usually 35 to 50), of whom 300,000 to 350,000 individuals are so classified, are capable of developing self-protection skills and mastering limited skills for semiproductive effort so they can contribute partially to their self-support if given an adequately protected environment. An estimated 3 children per 1,000 births will become moderately retarded, unlikely to progress beyond a mental age of 7 years even in adulthood.

Finally, the mildly retarded (IQ usually 50 to 70, but sometimes including those of slightly higher IQ), comprising the largest group of approximately 5 million retarded persons, are usually not distinguishable from normal individuals until school age when they are often identified by an inability to learn general school subjects. Without special attention, they often become the problem members of our society, capable only of a marginal productive role. They are the workers who are the most frequently displaced by the economic adjustments in our competitive society. However, given timely supervision, guidance, and training early enough in life, many will be capable of complete assimilation into our society. Minimally retarded persons are more nearly comparable to the nonretarded than they are to the most profoundly retarded. It is estimated that about 26 out of every 1,000 children born will be mildly retarded at some time in their lives.

The manifestation of mental retardation varies significantly among different age groups and also among different types of retardation. Only a small proportion of infants is identified as mentally retarded, because only gross defects are apparent and intellectual deficits which may show up later in life are not yet obvious. Many of the causative physical and environmental factors have not as yet had a chance to adversely affect the infant. By far the heaviest prevalence comes during the school age when more exacting requirements of behavior and intellectual performance are imposed. Some surveys of school population have shown that in the age group of 10 to 14, as high as 8 to 10 percent of the children appear to be mentally retarded. Then as these retarded individuals approach adulthood there is a tendency for many of them to be assimilated into the population and the differences to disappear. This helps explain why studies have found varying rates of retardation, ranging to as low as 1 percent of the population. The age-group figures cited are only rough estimates because there are no authoritative survey statistics available.

The key to prevention and correction of mental retardation is an adequate understanding of its causes. Medical and social sciences have made a substantial beginning in this direction. Within the past decade several previously unknown causes have been identified and means for their prevention have been discovered. Rapidly growing interest in the problem of mental retardation is producing a growing accumulation of data on the general conditions with which mental retardation is associated, even though the specific causes may not yet be fully evident. But much of the long road to full understanding of the complex phenomena involved lies ahead and indeed is not clearly defined as to the directions it may lead.

With present knowledge regarding the causal factors in mental retardation, it is possible to identify precise causes in approximately 15 to 25 percent of the cases. In such cases organic pathology as a result of disease or injuries is often demonstrable, most readily in instances where the degree of retardation is severe and there has been gross brain damage. There are a great many diseases and conditions which affect the brain and result in retardation, including infections or poisons in the mother's system during pregnancy, infection of the central nervous system during infancy, injuries to the brain at birth, head injuries in childhood, metabolic disorders determined by heredity, and abnormal brain growths.

Where specific causes have been ascertained, in many instances it has been possible to devise effective preventive action. Familiar examples include German measles in the first 3 months of pregnancy. RH blood factor incompatibility in newborn infants, lead poisoning, and dietary changes to overcome faulty body chemistry in such diseases as phenylketonuria and galactosemia.

Nevertheless, despite the recent progress made by medical science in identifying causes and developing preventive action for these specific causes, the hard fact is that the dramatic results flowing from new knowledge as yet apply only to part of the cases which can be specifically diagnosed and to only a small fraction of the total causes of mental retardation. For example, although medical science is now successful in averting brain damage in mental retardation due to RH blood factor incompatibility in practically all instances, the effect on the total situation is comparatively small because this cause accounted for about only 1 percent of the new admissions to institutions for the retarded. Phenylketonuria likewise accounts for only 1 of every 750 retarded, and galactosemia even less.

As matters stand, in from 75 percent to 85 percent of the cases of mental retardation, it is not yet possible to ascribe a specific diagnosis. This large group consists in the main of mildly retarded persons who show no gross abnormality of the brain.

But even here energetic research from many directions is casting light into the deep shadows. This research, from epidemiological surveys and other sources, strongly suggests that a variety of complex and interrelated factors in this category are definitely associated with the prevalence of mental retardation. It seems reasonable to believe that some members in this group are affected by operation of genetic and hereditary factors which are not yet clearly identifiable or understood. Similarly, a significant role for biomedical causes is suggested by data which show clearly that children born of mothers without prenatal care have an incidence of retardation many times greater than children born with proper maternal care. For example, a variety of unfavorable health factors, including lack of prenatal care, poor nutrition, deficient postnatal care,

and similar unfavorable factors, may produce damage to the brain or to the body which cannot be generally measured with present techniques but which will constitute a drag on physical and neurological development. Clearly, however, the incidence of mental retardation is heavily correlated with a lack of proper maternal and perinatal health care, which in turn is closely associated with the unfavorable socioeconomic status of families or whole neighborhoods or groups in the population.

The majority of the mentally retarded are the children of the more disadvantaged classes of our society. This extraordinary heavy prevalence in certain deprived population groups suggests a major causative role, in some way not yet fully delineated, for adverse social, economic, and cultural factors. These conditions may not only mean absence of the physical necessities of life, but the lack of opportunity and of motivation. A number of experiments with the education of presumably retarded children from slum neighborhoods strongly suggest that a predominant cause of mental retardation may be the lack of learning opportunities or absence of "intellectual vitamins" under these adverse environmental conditions. Deprivation in childhood of opportunities for learning intellectual skills, childhood emotional disorders which interfere with learning, or obscure motivational factors appear somehow to stunt young people intellectually during their developmental period. Whether the cause of retardation in a specific individual may turn out to be biomedical or environmental in character, there is highly suggestive evidence that the root causes of a great part of the problem of mental retardation are to be found in bad social and economic conditions as they effect individuals and families, and that correction of these fundamental conditions is necessary to prevent mental retardation successfully on a truly significant scale.

Whatever the causes, the failure of mentally retarded individuals to adjust successfully to social and economic conditions of our society constitutes a severe and growing handicap for the individual, for his family, and for the society. Moreover, as our competitive society becomes more complex and fast moving, the demands for intellectual capacity and for adaptability increase. Thus in an age of automation, individuals with minimal skills and abilities become doubly handicapped. Not only do they face an increasingly competitive society, but, hampered as they are, they must keep pace with people of increasingly higher capacities. Thus they become more easily submerged by the vicissitudes which others can surmount.

THE PREVENTION, TREATMENT, AND AMELIORATION OF MENTAL RETARDATION

From the available evidence on the prevalence and the causes of mental retardation, the Panel believes that the broad outlines and the directions in which action is needed can be determined with substantial assurance.

In the light of preceding discussion, a program of action must take account of the following facts: mental retardation is a complex phenomenon stemming from multiple causes. Many of the specific causes are known and can be prevented or their results can be treated. These are largely in the biomedical area.

For the great bulk of mental retardation cases, however, a specific cause cannot yet be ascribed with present knowledge. But epidemiological data from many reliable studies show a remarkably heavy correlation between the incidence of mental retardation, particularly in its milder manifestations, and the adverse social, economic, and cultural status of families and groups of our population. These are for the most part the low income groups—who often live in the slums and are frequently minority groups—where the mother and the children receive inadequate medical care, where family breakdown is common, where individuals are without motivation and opportunity and without adequate education. In short, the conditions which spawn many other health and social problems are to a large extent the same ones which generate the problem of mental retardation. To be successful in preventing mental retardation on a large scale, a broad attack on the fundamental adverse conditions will be necessary.

Another significant consideration in developing action programs is the lifelong character of mental retardation. Unlike other major afflictions, such as cancer or heart disease, which often come relatively late in life, mental retardation typically appears in childhood and always before adulthood. And once incurred, it is essentially a permanent handicap, at least at the present stage of biomedical knowledge. In this light, prevention—always desirable where

illness is concerned—assumes an even higher priority both in terms of the standpoint of general community measures and also of measures which the individual should take.

Still a third consideration looms large. Unfortunately we do not yet know the causes or the means of preventing but a fraction of mental retardation cases through biomedical means. Prevention of the great bulk of mental retardation cases will require measures to eliminate causative factors embedded in our social, economic, and cultural environment, and this will obviously take time. For many years we will still have the retarded with us and we will have to provide care and rehabilitation for them—care which must contain an increasing component of restorative services.

From these basic considerations the fundamental strategy of our battle against mental retardation takes shape. Because its causes are complex, our attack will have to be “broad spectrum” in character. We must act on many fronts, not only against the specific cause of mental retardation but against the root problems in the social, economic, and cultural environment which nourish the specific causes and seem to have a major and direct causative influence of their own.

Essentially this means that our society will have to allocate more resources to basic services to the youth of the land—for health, for education and training, for community reconstruction and renewal, and for improved employment and social services. In these efforts we must particularly strive to improve opportunities and services for distressed groups in the population.

Our campaign will be costly, but we cannot afford inaction. On economic grounds alone, the costs of caring for mentally retarded persons in institutions are 3 or 4 times the cost of rearing and educating normal children. Moreover, improvements in opportunities and services for our youth are likely to have beneficial effects for solving other pressing social problems. The same preventive measures which strike at the basic causes of mental retardation will also help to overcome other problems such as juvenile delinquency, mental illness, and general poor health and lack of fitness. For example, maternal health measures which avert the birth of mentally retarded children will also pay dividends in improving the general health of mothers and children. Educational opportunities which prevent mental retardation from setting in will also be useful in preventing school dropouts or combating juvenile delinquency. Thus such basic preventive measures are not only likely to be less costly in the end than the treatment and care of the retarded, but they assume a larger importance because of the other desirable benefits that flow from them.

Many new social measures have been spurred by Government action and private initiative during this century. They include numerous diverse and useful actions, including minimum wage laws, public health measures, improved educational services, and social security insurance programs, which help to alleviate the economic burden of care for the dependent. Many of these measures have a preventive effect on the conditions which engender mental retardation, while others help to provide the services or the financial support for which the mentally retarded benefit along with other people in the community. The continued existence of mental retardation on a vast scale, however, indicates that our society is still far from its goal of providing the essential conditions for normal healthy physical and intellectual development for this large segment of our children and youth. In this connection, it is significant that while Federal expenditures from budget and trust accounts for benefits and services for the aged are now on the order of \$15 or \$16 billion per year, the corresponding expenditures for children and youth are \$4 or \$5 billion.

THE NATIONAL ACTION PROGRAM TO COMBAT MENTAL RETARDATION

The Panel therefore urges high-priority consideration of necessary measures to improve and strengthen the health, the educational, and the social and community services for the youth of our land, particularly in instances where large concentrations of economically and culturally deprived families live. This is a sound and necessary course of action, not just because such services would directly benefit the mentally retarded, but because this is the only way which holds reasonable promise of preventing a large part of mental retardation from arising in the first instance. Increased outlays for the proper development of our human resources by giving all our children and youth a good start in life would represent a high-return investment which would pay dividends throughout the rest of their lives.

To attack a problem as pervasive and intertwined with fundamental social conditions as mental retardation, we must think and plan boldly. If, as it is apparent, the inadequate medical services available to large segments of our population during pregnancy and childhood play an important role in causing mental retardation, then we must remedy the basic situation of inadequate medical care. At a time when the infant mortality of some countries is reaching a new low, the infant mortality rate in the United States has leveled off at a relatively high rate. For example, it is now two-thirds higher than that of Sweden.

Likewise, we must have enough classrooms and teachers for all our students in order to provide adequate educational services to the mentally retarded. Although we have made excellent progress in providing increases in special educational facilities for the retarded, the shortages of classrooms and of teachers, which are evident in education generally, are even more aggravated in this area.

In addition to taking vigorous national action to improve the general programs, we must recognize that the mentally retarded who are in our population represent a group with extraordinary needs. Society's special responsibility to persons with extraordinary needs including the retarded is (1) to permit and actually foster the development of their maximum capacity and thus bring them as close to the main stream of independence and "normalcy" as possible; and (2) to provide some accommodation or adjustment in our society for those disabilities which cannot be overcome.

In the first of these two categories are such services as health care, guidance, special education, vocational rehabilitation, and the like, directed to groups especially prone to mental retardation or who are afflicted by it. Nowhere in our society are there more opportunities for constructive and useful innovation than in the development of improved techniques, better services, and improved institutional arrangements for the effective integration of such handicapped individuals into a self-reliant, productive, and happy life in our society.

The second part of the task concerns the provision of adequate and improved facilities for the care of the retarded individuals who must be maintained in institutions. Here, too, a positive and hopeful emphasis is possible and necessary, because improved methods and effective techniques can contribute immensely not only to the welfare of retarded persons as individuals but also can help them become at least partially self-maintaining.

Underlying effective action on all these fronts as they relate to retardation, there is the need for increased and more exact knowledge regarding the causes of retardation and the methods of prevention and care. More research support and capacity is therefore necessary not only specifically with respect to the mentally retarded but in the basic areas of health, learning processes, and other fundamental human processes which will apply to all people alike. The gaining of new fundamental knowledge can benefit not only the U.S. citizenry but all of mankind.

Thus, considering the problem of the mentally retarded in its broadest aspects, the Panel has addressed itself to both sides of the equation: (1) the necessary improvement of basic services to all people, and (2) to improved specific services to the mentally retarded. The Panel recognizes that extreme shortages of trained personnel and of funds will not make it possible to increase services and facilities greatly overnight. We must plan our campaign to combat mental retardation not for just next month or next year, but for the next decade. And we must move ahead vigorously and imaginatively. In this context, the main recommendations of the report are directed to—

1. Research in the causes of retardation and in methods of care, rehabilitation, and learning.
2. Preventive health measures including (a) a greatly strengthened program of maternal and infant care directed first at the centers of population where prematurity and the rate of "damaged" children are high; (b) protection against such known hazards to pregnancy as radiation and harmful drugs; and (c) extended diagnostic and screening services.
3. Strengthened educational programs generally and extended and enriched programs of special education in public and private schools closely coordinated with vocational guidance, vocational rehabilitation, and specific training and preparation for employment; education for the adult mentally retarded, and workshops geared to their needs.
4. More comprehensive and improved clinical and social services.

5. Improved methods and facilities for care, with emphasis on the home and the development of a wide range of local community facilities.

6. A new legal, as well as social, concept of the retarded, including a protection of their civil rights; life guardianship provisions when needed; an enlightened attitude on the part of the law and the courts; and clarification of the theory of responsibility in criminal acts.

7. Helping overcome the serious problems of manpower as they affect the entire field of science and every type of service through extended programs of recruiting with fellowships, and increased opportunities for graduate students, and those preparing for the professions to observe and learn at first-hand about the phenomenon of retardation. Because there will never be a fully adequate supply of personnel in this field and for other cogent reasons, the Panel has emphasized the need for more volunteers in health, recreation, and welfare activities, and for a Domestic Peace Corps to stimulate voluntary service.

8. Programs of education and information to increase public awareness of the problem of mental retardation.

In addition to a strong emphasis on research and prevention, the report recommends—

1. That programs for the retarded, including modern day care, recreation, residential services, and ample educational and vocational opportunities, be comprehensive.

2. That they operate in or close to the communities where the retarded live—that is, that they be community centered.

3. That services be so organized as to provide a central or fixed point for the guidance, assistance, and protection of retarded persons if and when needed, and to assure a sufficient array or continuum of services to meet different types of need.

4. That private agencies as well as public agencies at the local, State, and Federal level continue to provide resources and to increase them for this worthy purpose. While the Federal Government can assist, the principal responsibility for financing and improving services for the mentally retarded must continue to be borne by States and local communities.

One may well ask how these broad objectives for the retarded differ in kind or degree from desirable goals for others. They do not differ fundamentally, but the retarded do not presently receive either the attention or the services accorded to other groups with special needs. An effective way to achieve results beneficial to many is to seize the handle presented by an important segment of the population which has been neglected and lift that group to a higher level without losing sight of the needs of others. If, for example, research in learning is spurred by the urgent and specific needs of the retarded, the chances of gaining information of a generic nature applicable to all will most certainly be enhanced.

THE PANEL'S WORK AND ITS REPORT

In carrying out its mandate, the Panel has employed four main methods of study and inquiry:

1. Task forces on specific subjects were appointed to which all members of the Panel were assigned; special advisers were designated to work closely with them.

2. Public hearings were held in seven major cities of the country to which public officials concerned with mental retardation, teachers, representatives of several professions, parents, and others were invited not only to report on local and State programs and gaps in service but to make recommendations to the Panel.

3. Panel members and advisers visited England, Sweden, Denmark, Holland, and the Soviet Union to study methods of care and education of the retarded and to become acquainted with research in those countries.

4. A considerable body of literature and the results of recent studies were reviewed; and members of the Panel visited and observed facilities and programs for the retarded in several States.

A report of this type must be regarded as only one step in a process. In this instance the "process" may be said to have started with a heightened activity within the American Association on Mental Deficiency dating from the close of World War II, and the upsurge of interest among parents leading to the founding of the National Association for Retarded Children. The support of the Congress and the subsequent emphasis on development of programs for the retarded in

the Department of Health, Education, and Welfare were additional steps of major importance.

In appointing the Panel on Mental Retardation, the President recognized the emergence of an idea "whose time had arrived" and gave impetus and visibility to a complex problem that had not yet been brought into the full view of the country.

The next steps beyond the submission of this report are, of course, the task of implementation, interpretation, and public education; and legislative activity and funding at the local, State, and Federal levels. Each of the several sections of the report presents some basic "state of the Nation" data and opinion as to the present status of the subject area under discussion, and makes both specific and general recommendations designed to fill in existing gaps, and to improve or extend an essential service or develop a new program. In each instance it is made clear where the responsibility for action lies, whether in the locality, in the State or Federal Government, with private agencies or in some combination of these, as is so often the case.

A substantial number of problems discussed in the report require further study and most of the recommendations call for a vigorous followup. Studies must be supported and a followup program set in motion but, in the meantime, we must go forward on the basis of past experience and with the tools at hand.

Robert Frost once defined wisdom as that quality which motivates man to act in spite of insufficient knowledge. We must move ahead in mental retardation, although we lack conclusive knowledge and all the tools we need: but we must continue to search, to learn, and to gain new insights if the decade ahead is to be one of steady progress and high achievement.

In acknowledging the cooperation of the personnel in the Department of Health, Education, and Welfare, the Panel wishes to record its appreciation of the progress made by the several agencies of the Department in developing programs of benefit to the mentally retarded. The staff and members of the National Association for Retarded Children and the American Association on Mental Deficiency have been untiring in their assistance to the Panel; State departments, private health and welfare agencies, professional organizations, parent groups, and countless individuals have cooperated both as private citizens and as formal advisers. All have contributed substantially to this enterprise and we are grateful to them. The knowledge that influential Members of the Congress have had a long and active interest in the field of mental retardation has been a source of encouragement and inspiration to the Panel. Their leadership, moreover, has been a major factor in the constructive developments that have taken place in the field to date.

TIME SCHEDULE FOR REPORTING

Mr. FOGARTY. I think it was an excellent report. I have talked to members on the President's Panel who thought that they could have done a better job if they had a little more time.

That was the only fault that I heard from people who served on the Committee. They just had a year, was it not?

Dr. MASLAND. Yes, they worked under tremendous pressure.

Mr. FOGARTY. I know. That was the only complaint that I heard about it was that they should have had a little more time to complete the report.

What are some of the things that might have been in it that you can think of if they had had a little more time? I never did get around to specifics with the two or three who had this complaint.

Dr. MASLAND. Their recommendations cover some very broad fields. Of course, my own orientation and that of this Institute are directed very specifically toward the problems of brain damage and injury of the nervous system which we feel underlie a great deal more mental retardation than is generally recognized.

I think that there is needed a much greater emphasis in the study of the mechanisms through which the brain is injured before and after birth, and of the relationship between the structure of the brain and the consequent disturbance of performance.

Mr. FOGARTY. Who ought to be doing some of this work?

INSTITUTE'S PLANS FOR MENTAL RETARDATION RESEARCH

Dr. MASLAND. The major responsibility, I think, for this particular facet rests with our Institute.

Mr. FOGARTY. I see.

Do you have any plans for 1964?

Supply for the record a suggested plan for 1964 in this area.

Dr. MASLAND. All right.

Mr. FOGARTY. And how much you think could be efficiently used to support a start in this direction?

(The information follows:)

NINDB'S PLANS IN MENTAL RETARDATION FOR 1964

Since its establishment slightly more than a decade ago, much of the Institute's broad program for the study of the brain and its diseases has related directly or indirectly to the problem of mental retardation. Within this program it is most difficult to draw a meaningful distinction between activities which do and do not relate to mental retardation. It is the mission of this Institute to foster the study of the nervous system and its diseases. Mental retardation is a manifestation of disease or dysfunction of the brain. To the extent that the Institute's program is contributing to the understanding of the brain, its functions, and its diseases, it is contributing to the understanding of mental retardation.

Studies which focus upon one neurological disease often relate to several others. For example, in kernicterus, combinations of mental retardation, cerebral palsy or epilepsy, blindness and deafness, are more often the rule than the exception. In later life, neurological impairments from head injuries, infectious or vascular diseases of the brain can arrest or destroy mental development. Clearly, research in mental retardation is an integral part of a research attack on a host of neurological disorders. Conversely, research on other neurological disorders, or on the structure and function of the brain and nervous system are integral parts of a research attack on mental retardation.

From its inception, the National Institute of Neurological Diseases and Blindness has regarded the knowledge of the underlying structure and function of the brain, nervous, and sensory systems as essential to progress in prevention and treatment of neurological disorders, of which mental retardation is one symptom. Although the special emphasis on the part of the Congress, in 1956, spearheaded the formalization of a research program on mental retardation, this basic philosophy has not been altered. Consequently, the Institute's program in mental retardation—especially its causes, diagnosis, treatment, and prevention—encompasses research on the basic structure and function of the neurological and sensory systems; clinical studies of the perinatal period and the manifestations of the disorders in patients; experimental animal and laboratory studies; and the development and training of specialized manpower to work in the multiple aspects of these areas.

Training: The most serious problem in neurology is manpower. During the early decades of this century, and in fact until the Congress launched the program of this Institute in the early 1950's, the study of the nervous system was becoming almost extinct. Lack of interest, the complexity of the problem, inadequate methodologies, and the glamor of psychoanalysis had all served to create a shift of emphasis away from the exacting demands of the neurological sciences.

The launching of the training program of the Institute of Neurology has been paralleled by the rapid evolution of new methods and techniques. A fantastic growth has resulted. The number of supported training programs in the neu-

rological sciences has increased from 15 in 1954 to over 120 in 1962. Between 1961 and 1963, the number of trainees in clinical and basic neurology and in neurosurgery has increased from 390 to 579. During this brief 2-year period, the number of men in training in the basic science programs has more than doubled—from 91 to 185. The resurgence of interest is such that trainees have scarcely completed their training before they are being called upon to launch new training programs of their own. We are, in fact, in the tooling-up phase of a tremendous attack.

It is to the men who are beginning to stream from Institute training programs that we must turn for our knowledge of the structural basis of neural activity—the intricate basic mechanisms which underlie all intellectual processes; for an understanding of the impact upon these structures of disease and injury; and for a careful diagnosis and treatment of the many conditions whose ravages leave the brain and intellect in disrepair. Furthermore, if ever a means is to be found for the structural restoration of the brain, it must come from men who have an intimate knowledge of its nature.

During the latter part of this past fiscal year, the Institute launched an extension of its clinical training programs specifically to encompass training for public health activities. This Institute will support the training of specialists to man the much-needed diagnostic centers which will provide precise evaluation and medical treatment for children and adults with neurosensory disabilities and diseases. In addition, developmental or undergraduate training grants will be created to establish a focal point for neurological and sensory training in every medical school in the country. At this stage of development, \$15 million could be used in fiscal 1964 for this rapidly expanding program.

Perinatal studies: A very high proportion of neurological and sensory disabilities, including mental retardation, have their origin at, or prior to, birth. For this reason, in 1956, the Congress directed this Institute to launch a program for the investigation of the perinatal causes of cerebral palsy, mental retardation, and other neurological and sensory disorders of childhood. A status report of the "collaborative project" requested by the committee is appended.

The collaborative project is attempting to fill a number of needs within the field of mental retardation. It is seeking—

- (1) To determine the perinatal causes of mental retardation, including (a) the factors of pregnancy which are likely to lead to unfavorable outcome, in order that these factors may be avoided and women given the special care needed to prevent such outcome; (b) the effects of drugs, treatments, and procedures, employed during pregnancy and at delivery; and (c) the impact upon the developing individual of postnatal physical, social, and environmental factors.

- (2) To determine the earliest signs and symptoms of neonatal distress or disease in order that prompt preventive measures may be instituted;

- (3) To determine the earliest evidences of physical and intellectual deviation in the developing child in order that prompt and specific remedial measures can be applied; and

- (4) To observe the effects of physical and intellectual deviations upon the physical, intellectual, and behavioral characteristics and development of the child.

During the fiscal year 1964, it is anticipated that grants to the collaborating institutions for this project will require approximately \$7 million. Within the budget we have submitted there is an allocation of \$2,228,000 in direct operations for this project. The Institute has assumed direct responsibility for the data processing essential to this study. At the present time, the rapid analysis and dissemination of the wealth of research information already assembled is being delayed through such lack of resources as outlined in subsequent testimony. A figure of \$2.8 million for the central office of the collaborative project would include an increase of \$572,000 to make it possible for data processing to keep pace with the extramural aspects of this investigation.

Other perinatal studies: In addition to the major collaborative perinatal study, the Institute is expanding its programs of independent studies utilizing data from the larger study; complementing the project by various other clinical and laboratory studies of perinatal factors through investigators not directly associated with the collaborative project; and accelerating its program of perinatal physiology in Puerto Rico.

In an effort to examine special populations and to emphasize greater details than could be included in the collaborative project, the Institute is supporting a similar study at the Kaiser Permanente Foundation in San Francisco to observe

approximately 4,000 deliveries per year. This and similar investigations could operate at a level of approximately \$7 million in 1964.

The Institute's laboratories of perinatal physiology on Puerto Rico were established in 1956 in order to study in animals the processes which are producing neurological and sensory defects, including mental retardation, in humans. These laboratories have a colony of more than 800 monkeys, a large proportion of which are breeding animals maintained for studies of pregnancy. Investigations carried out in this laboratory have already made important contributions to our knowledge of the mechanisms by which neonatal asphyxia and jaundice are producing irremedial brain damage leading to cerebral palsy and mental retardation in babies. Last year, the Congress appropriated funds for the construction of a new facility for this program. In 1964, operating funds of \$754,000 will be required.

It must be emphasized that the current projects outlined above represent only a limited number of clearly defined programs developed by the Institute to focus on certain specific aspects of the problem of mental retardation. The Institute's contribution to the study of mental retardation, however, is far more extensive. Thus, within the Institute's general program in 1964 are included \$7.4 million for the study of the anatomy, chemistry, physiology, and pathology of the brain. Much of this work is directly related to mental retardation. Clinical studies include \$3.4 million for epilepsy—a complication which afflicts as many as 20 percent of the retarded in some of our State institutions. Disabilities of speech and hearing are another frequent and severe aspect of retardation. The Institute's program includes almost \$5 million in this general area.

In addition to the current programs, at the request of the committee, a number of suggested programs are outlined in subsequent testimony in an Institute statement relating to the President's Panel on Mental Retardation. These include an extension and further utilization of present perinatal studies, the development of a national neurosensory instrumentation center, virus screening programs, head injury centers, and neurological disease oriented centers.

These few illustrations of the Institute's current and planned programs not only summarize certain program facets but also indicate, in a very real sense, that almost the entire program of the National Institute of Neurological Diseases and Blindness has a direct relevance to the vast problem of mental retardation.

Mr. FOGARTY. What other areas do you think we ought to be thinking about or looking at?

Dr. MASLAND. In relation to the total program of the Institute?

Mr. FOGARTY. I am thinking of the area of mental retardation and cerebral palsy. I was going to ask you specifically about cerebral palsy.

COMMENTS ON REPORT OF PRESIDENT'S PANEL ON MENTAL RETARDATION

What else in mental retardation that was not gone into thoroughly by the President's Panel, might well have more study?

Dr. MASLAND. I would like to think that over and prepare something for you.

Mr. FOGARTY. All right. Do that.

(The information follows:)

COMMENTS ON THE PRESIDENT'S PANEL ON MENTAL RETARDATION

The report of the President's Panel on Mental Retardation represents a most exhaustive and thoughtful review of the many medical and social problems which mental retardation presents. Possibly it is the very breadth of this problem that has prevented the panel from highlighting one essential and fundamental fact. The underlying element of all intellectual and neural activity is the structure within which these activities are centered—the brain. Our ultimate understanding of the problem of mental retardation will never be complete until we have a clear picture of the structure, organization, and mode of action of the central nervous system, and of the impact upon it of the many organic diseases, either prior or subsequent to birth, which may damage the brain's intricate mechanisms.

Members of the Institute's staff and of its Advisory Council have expressed serious concern over what appears to be a general lack of appreciation of the important role which the study of the nervous system must play. In the special report submitted above, we have emphasized the extent to which the Institute's total program is responsive to the need for strengthening this aspect of our approach to the problem of mental retardation.

There are certain aspects of the Institute's program which might have been the subject of specific recommendations if time had permitted the Panel to study them in detail. In addition, several exciting possibilities for new programs appear to have been overlooked.

1. PERINATAL RESEARCH

The report of the Panel makes reference to some of the early findings of the collaborative perinatal project of this Institute. It points to some of its results as "illustrative of research findings which have led to prevention of a significant number of cases of mental retardation." However, the Panel makes no recommendation for continuation or extension of this important undertaking—an undertaking which has mobilized vast resources in 15 university centers, and has created a national resource with continuing capability for an organized and concerted drive against the causes of retardation, cerebral palsy, and other neurological and sensory disorders. The potential of this resource is largely unexplored, but numerous requests from many agencies indicate that this unique program is in a position to make broad contributions to many facets of the problem of mental retardation.

At the present time, a wealth of research information is already assembled in the collaborative project. The Institute is now exploring with other agencies the most profitable directions for the further extension of this program and should be in a position to present such a broad plan for fiscal year 1965.

2. ROLE OF VIRUSES IN PREGNANCY

The Panel points out that a "number of viruses and other infectious agents have already been identified or are strongly suspected of producing damage to the fetal brain when the mother is infected during pregnancy." No specific recommendation for an attack on this problem is made, however.

Within the Institute's collaborative perinatal project, every woman is receiving serological examinations for the detection of viral infection. Preliminary studies show that about 7 percent of these women experience infection by a known virus during pregnancy. Within this program, the virus of German measles—an agent known to produce mental retardation—has been isolated. The human disease has been produced experimentally for the first time. The effectiveness of a vaccine has been demonstrated, and its usefulness in preventing fetal injury is under investigation in monkeys.

These studies should be extended to other viruses. The place to search for such viruses is in abortions or premature births because those agents which in mild instance cause mental retardation, lead to death and miscarriage of the fetus in severe cases.

The methods for culturing such viruses have now become routine, but they are laborious and time consuming. Such work does not provide challenge for the university-based scientist whose interest lies in the search for new approaches. It would be possible, however, through industrial contracts, to establish a large screening program to search for viruses among a number of specimens. Within such a program it is almost certain that additional viruses responsible for fetal injury would be found.

3. A NATIONAL NEUROSENSORY INSTRUMENTATION CENTER

Because of the complexity of the nervous system, the development of precise instruments is an essential aid to investigation. For example, a statement frequently quoted is that "in 75 percent of instances of mental retardation no structural abnormality of the brain has been demonstrated." A thorough review of the literature suggests one probable explanation for this impression: brains of retarded individuals after death have not been studied with the precise methods required to demonstrate detailed and deep-lying deformities.

The studies of Dr. Windle and his associates in Puerto Rico indicate that asphyxiated newborn monkeys undergo extensive cell loss in the brain. Such loss, however, is demonstrable in later life only as a reduction in the number of cellular elements present. One cannot see what is absent, and without the use of precise cell-counting techniques, up to 25 percent of the neural elements of a nucleus of the brain may be lost without this being evident to the neuropathologist.

Studies in the Institute's Laboratory of Perinatal Physiology also indicate that the effects of such deleterious agents as asphyxia and kernicterus are highly selective, leading to serious impairment of some parts of the brain while sparing others. Exact quantitation of cell loss in various nuclei of the brain is thus essential if we are to understand the structural basis of the varied forms of intellectual impairment in mental retardation. However, the brain comprises several billions of nerve cells. It has been the lifework of a few dedicated scientists to attempt such quantitative studies of even one or two specimens. However, technology has now reached the stage where much of this arduous task could be accomplished automatically by the use of instruments. The development of an automatic cell-counting microscope is now well within the realm of attainment. The specific technological problems which must be overcome in the production of such an instrument have been defined.

A central planning group, empowered to use grants or contracts to recruit the technical and industrial resources required, is need to make this possibility a reality. The availability of a cell-counting instrument to scan the brains of mentally retarded individuals dying of intercurrent diseases, and of animals with comparable experimentally induced neurosensory defects, would constitute a major contribution in our efforts to define with accuracy the organic abnormalities responsible for mental retardation.

Particular concern has been expressed regarding the complex problem presented by the blind and the deaf retarded. Especially where multiple handicaps are present, the mobilization of the individual's intellectual resources may be completely blocked by failure of communication. Fundamental investigations, well underway, are exploring the use of patterned sensory stimuli, applied to the skin by electronic devices, as a means of establishing a meaningful communication. In a similar way, Helen Keller learned the meaning of sound through feeling with her fingertips the vibrations of the larynx of her teacher. The time is ripe for an all-out investigation of the various alternative sensory pathways through which visual and auditory information may be made available and meaningful to those whose normal channels are destroyed.

An even greater challenge exists in explorations directed toward the substitution of electronic devices for the eye and the ear—devices which might be keyed into the human nervous system directly in such a fashion as to provide substitute stimuli within the visual and auditory systems. The problems to be overcome are awesome but not insurmountable.

In vision, for example, one first must have precise knowledge of the coding process of the eye whereby the light impulse falling on the retina—composed of some 100 million computer cells—is converted into patterns of nerve impulses. When this knowledge is available, it will be necessary to develop computers and other instruments capable of interpreting the impulses. Finally, means must be found to key the coded messages into the nervous system in a way which will not destroy the delicate nerve fibers to be stimulated.

A committee of competent scientists is actively engaged in the consideration of this entire problem of substitutions for vision. The financial and logistical resources required to transform into reality the ideas of this committee, and of other related groups, should be established within a national neurosensory service center.

4. A COOPERATIVE HEAD INJURY STUDY

The most common single cause of hospitalization of children is accident and injury. Of a group of injured hospitalized children, 30 percent were found to be suffering from injuries of the head and brain. Head injury is not ordinarily thought of as a cause of mental retardation. However, in approximately 10 percent of institutionalized retarded, a postnatal condition is held responsible for the retardation. Among these, a significant number result from head injury. Automobile accidents account for a large portion of such accidents, but sports, various play activities, and home accidents are also causes. As pointed out by the President's Panel, the obvious solution is prevention. However, as is the

case with asphyxia, many of the serious permanent residuals of head injury appear to develop after the event during a postconcussion reactive phase. Therefore, effective management of this delayed reaction could materially reduce the severity of the permanent neurological damage in many instances of head injury.

A cooperative head injury program should investigate many problems: the logistical problems of providing prompt, definitive surgical management of accident victims from cities and highways; the fundamental characteristics of the reaction of the brain to injury; the classification and evaluation of the injured; and the evaluation of the therapeutic measures now being carried out on a largely empirical basis.

5. CENTERS TO STUDY DISEASES OF THE NERVOUS SYSTEM IN INFANCY AND CHILDHOOD

The problem of mental retardation is one of broad scope to which a diversity of skills and talents must be addressed. The Chairman of the President's Panel has made it clear that it has been the intent of that Panel to mobilize, for the attack on this problem, individuals having the widest possible variety of skills. Important among these is the scientist whose life is devoted to the study of the brain. The mobilization of the field of neurology to attack this vast problem requires a clear definition of the role and responsibility of clinical neurologists, neuropathologists, neurophysiologists, neurochemists, and neuroanatomists. The importance of this aspect of the problem of retardation requires that it receive specific focus. The development of centers specifically to study diseases of the nervous system in infancy and childhood, is essential if such people are to be drawn into active participation in research in this field.

It is believed that the above-mentioned special activities are in line with the thinking and objectives of the President's Panel and could appropriately have been included within their report.

CEREBRAL PALSY

Mr. FOGARTY. What about cerebral palsy? What are you doing and what is there new to report?

Dr. MASLAND. Our orientation has been to tie the program for mental retardation and the program for cerebral palsy very closely together. The reason is that the prenatal causes of the two conditions are quite similar. Furthermore, a considerable proportion of the individuals who are severely retarded mentally have cerebral palsy as well and a considerable proportion of cerebral palsy children have some degree of mental retardation.

Thus, the collaborative project is also our major emphasis in the program of cerebral palsy.

We are involved in a certain number of studies more specifically directed toward this. I think our program in Puerto Rico is quite relevant.

PUERTO RICO LABORATORY PROGRAMS

Mr. FOGARTY. What is the extent of collaboration between the laboratory in Puerto Rico and the various groups in the clinical collaborative program on mentally retarded and cerebral palsy supported by your Institute?

Dr. MASLAND. These two programs are complementary to each other. That is, within the group of pregnant women we discover certain problems which cannot be dealt with by experimentation on humans. Under those circumstances we turn to the laboratory in Puerto Rico to do the experiments in monkeys. Conversely from the experiences in Puerto Rico, there are derived important conclusions which are proven in monkeys but may not apply to humans. By the exploration within the collaborative project, we can determine these questions.

As far as the working relationships are concerned, we do have what you may call an overlapping directorate. That is, Dr. Berendes, who is the chief of the perinatal research activities of the collaborative project, is also a member of the advisory board of the Puerto Rico project. He thus has knowledge of what is involved in both operations. Obviously, I and other members of my staff also serve in a coordinating role. In addition, a number of the people who have worked in the laboratory at Puerto Rico are from our collaborating institutions.

VIRUSES IN PREGNANCY

As an example of the way these things operate, Dr. Sever works in the collaborative project in the program having to do with the search for viruses in pregnancy. He became involved with the study of German measles. A virus was isolated from patients with German measles and the question arose, "Is this virus actually capable of causing a human disease?"

One way to find out would be to find volunteers and inject the virus into them. But instead of doing this, Dr. Sever went to Puerto Rico where we had monkeys that were naturally free of viruses. We knew they were probably not immune.

Those animals were infected with the suspected virus and they developed a mild illness. Following recovery, antibodies against this new virus were discovered. It was subsequent to this that Dr. Sever then proceeded to test this virus with human volunteers and experimentally produced German measles.

Now he is carrying his studies further in Puerto Rico and attempting to find out whether this virus will produce in monkeys congenital malformations which are similar to those we see in humans.

COMMUNICATION WITH COLLABORATIVE PROJECT

Looking at this from the reverse point of view, Dr. Windle and his group in Puerto Rico are making some very important investigations of the injury to the nervous system which occurs as a result of jaundice of the newborn.

He and his collaborators, including Dr. Lucey from Boston, have discovered that if an animal is asphyxiated and then is subjected to a high level of bile pigment, the brain is injured. But the high level of bilirubin, itself, is not capable of causing damage. It requires the combination of these two factors. It is necessary for us to review the data from the collaborative project to find out whether, in fact, the individuals in the project who are damaged were individuals who suffered both bilirubinemia and asphyxia.

This is the type of back and forth operation which is involved but there is not a formal planning operation between the two groups. I think this would be a desirable thing to do.

Mr. FOGARTY. That was the impression I received when the committee went down there a few months ago, that there was a lack of communication between that project and your collaborative study.

It did not seem to me that the people in Puerto Rico knew what you have told the committee this morning about your collaborative study.

Dr. MASLAND. That is right.

Mr. FOGARTY. As far as I could gather there are not many of these collaborative centers which knew what was going on or what had happened in this study in Puerto Rico. Are you going to try to do something about it?

Dr. MASLAND. It would be quite feasible for us to bring these people together. We have a big scientific meeting of the project this spring. The collaborators have reviewed over 100 different facets that could have been analyzed but because of the problems of data processing—the fact that this takes time—at this time they limited it to some 20 different papers which will be reported at this scientific session. This meeting could very easily include some report from Puerto Rico which would bring those people together.

Mr. FOGARTY. When the new laboratory building is completed at the new center down there, are these experiments going to be moved into this new building?

Dr. MASLAND. Yes, sir.

HOUSING PROBLEM

Mr. FOGARTY. They tell me that they have a problem in housing in this particular area. Has any thought been given to this problem?

Dr. MASLAND. It would be of tremendous value to the project if a means could be found for establishing a small housing facility where the people in Puerto Rico could stay. This is bound to be a place where many visitors will come.

Mr. FOGARTY. They were talking about the visitors.

Dr. MASLAND. Yes. Much of the work is being done by people who come for 1 or more weeks.

In fact, this is the advantage of this facility. We have everything ready and an outstanding man from any part of the world may come for a period of a month, run over a great series of experiments and then spend the next year working over the data. Two or three of the men who have come have indicated that they accomplished more in 1 month in Puerto Rico than they could have accomplished in 2 or 3 years of regular work.

Mr. FOGARTY. We were told that housing was provided for the middle American research unit.

Dr. MASLAND. I think that would be a tremendously valuable feature of this operation.

Dr. SHANNON. The middle America project is on federally leased property and it ties in with the quarters system for the Panama Department of the Army, for civil aeronautics, and the like. We actually have a segment of a housing development that was set up for civil aeronautics. Puerto Rico, on the other hand, is part of the United States. The laboratory will be on university grounds and the Federal Government would have to purchase land in addition to building housing.

Mr. FOGARTY. Why could not a certain number of domiciliary rooms be built in the research building that is going to be built?

Dr. SHANNON. This is not NIH property. This is a university campus. While that type of housing might satisfy the transients, it would not satisfy the need for the stable, permanent group of scientists.

I would just like to add one thing. While the provision for visiting scientists is excellent, I would say that too much of available resources have been placed at visiting scientists' disposal and too little at the disposal of the full-time employees upon which the total, long-term results depend. These are the people who are much more needful of housing than the visitors.

Mr. FOGARTY. Well, I hope you do something to provide at least a few living units there.

AMELIORATING BRAIN DAMAGE FROM ASPHYXIA

Doctor, we were told about the work they are doing down there, ameliorating brain damage, that might be caused at birth.

How is that coming along?

Dr. MASLAND. It is a very important investigation. The key issue here is the discovery that much of the brain damage which results from asphyxia takes place following asphyxia, and not actually during the period of time that the child is suffocating. Apparently, the period of asphyxiation sets in motion a chain of events which continues over a period of several days. The capillaries have changes in their permeability so the fluid leaks out into the tissue, and the subsequent swelling of the brain probably causes more damage than does the actual period of deprivation of oxygen.

This means that by finding a method to interrupt this process, it may be possible to ameliorate the effects of the asphyxia after the period of exposure has taken place. This is the approach that Dr. Windle and his associates are making. They have come to the conclusion that changes in the sugar and the acidity of the blood are very important factors in this process. They are attempting to reverse this by giving alkali or sugars. They have not yet conducted enough experiments to be certain whether this will really work but, from their preliminary observations, they are quite hopeful.

I might say that this has been done elsewhere, also, in children with somewhat similar results.

Mr. FOGARTY. We were also told that they were trying to induce kernicterus in newborn monkeys.

Dr. MASLAND. Yes.

Mr. FOGARTY. Because they had been able to work with only one kind of injury before.

Dr. MASLAND. That is right.

They have actually produced kernicterus by a combination of asphyxia and by giving large amounts of bile pigments.

Mr. FOGARTY. This is quite an important study.

Dr. MASLAND. It is a very important development, yes.

Another important area which they have been investigating, in collaboration with the outstanding South American scientist, Dr. Caldero, has had to do with the effect of uterine contraction on the baby's head. They now have very precise information regarding the effect of deviations of uterine motility on the baby's health.

This relates very closely to the use of certain drugs to induce delivery, and highlights the necessity for using these drugs with extreme care, if at all, because of the danger that a sustained contraction of the uterus may be produced and result in injury to the nervous system.

NEED FOR FULL-TIME DIRECTOR

Mr. FOGARTY. Have you given any thought to the problem of the Director of this program in Puerto Rico spending half of his time there, and half of his time in Bethesda?

Dr. MASLAND. Yes, we have been very much concerned over the fact that this project has not had a full-time, top-level representative of the Institute in Puerto Rico and we have discussed with Dr. Pearce Bailey, the former Director of this Institute, the possibility that he might undertake to represent the Institute in Puerto Rico.

Of course, he is very closely advised regarding the Institute's program. The project in Puerto Rico was launched under his direction so that he has been close to it from the very beginning.

STANFORD STUDY ON EARLY TESTING FOR MENTAL RETARDATION

Mr. FOGARTY. Doctor, are you familiar with this research program carried on by the Department of Education at Stanford?

Dr. MASLAND. Just superficially.

Mr. FOGARTY. We were told by the people in cooperative research, that they gave a grant to this school to try to determine mental retardation at an earlier age. Mr. Ianni is the man who told us about this.

He said:

Because of this grant, we have been able to devise a test to identify them as young as 22 months of age, and this test remains valid up to the age of 18.

Dr. MASLAND. I am not acquainted with that work.

Mr. FOGARTY. I'll read some more of the transcript of that hearing because it has such a close relationship to some of the Institute's work.

Mr. IANNI. Following early identification is a second problem. Should they be placed in special classes? This has been a controversy.

Mr. FOGARTY. How do you identify them?

Mr. IANNI. We have two different studies in this area. One is through a series of picture tests. This can be used with the 22-month-old child. But through the series of tests we have been able to measure how the child learns simple tasks. Those retarded have difficulty in two respects. One, in learning the simple task and second, in transferring the learning of that simple task to a more complex task.

Mr. FOGARTY. Was this considered in the survey study made by the President's Committee on Mental Retardation?

Mr. IANNI. I do not think so, sir. This is still basic research, and has not been tested in a large number of situations.

Mr. FOGARTY. I see. I read the report and I did not remember anything like this in the report.

It is basic research.

Mr. IANNI. That is right.

Mr. FOGARTY. But you are satisfied that it is satisfactory?

Mr. IANNI. We are satisfied enough with it that we would like to proceed with more research and test it in a large number of situations.

Mr. FOGARTY. How many have you tested? How many places have you—

Mr. IANNI. It has only been developed at one institution at the present time.

Mr. FOGARTY. I see. You want to try it in other institutions?

Mr. IANNI. Just as, again, in Salk vaccine. It was necessary to field test it in a lot of cases. We feel this is the way to work in every situation.

Mr. FOGARTY. What do you mean, field test it?

Mr. IANNI. Once the vaccine was developed, the next stage was setting up a large number of tests in different parts of the country, inoculating a large number of children, and then following these children through.

Mr. FOGARTY. I see.

Mr. IANNI. We should do this also in educational research, because very often these materials are developed in a laboratory school at a university which has very small classes with very specialized children, highly paid teachers. Because it works at Stanford Laboratory School, this does not necessarily mean that it is going to work in some small community in Ohio, for example.

Mr. FOGARTY. Yes; I understand that.

Mr. IANNI. And the subject test.

Mr. FOGARTY. I think that is a very worthwhile project.

Mr. IANNI. A second project in this area, which I think has even more promise concerning the long-standing controversy as to whether special classes are of benefit to mentally retarded children. The argument has usually been that they do learn better in these situations, but because they are placed with other mentally retarded children, this has a bad social effect upon them. We have a study at the present time, which has been following two groups of mentally retarded children; one group with special classes and the other group in a regular class. They have been followed for 3 years now.

Mr. FOGARTY. Where is that?

Mr. IANNI. Illinois. And they have conclusive results. Not only do the children learn better in the special classes but their social adjustment is considerably better because they are able to work with each other.

Mr. FOGARTY. In special classes?

Mr. IANNI. Yes, sir.

Mr. FOGARTY. I see.

Mr. IANNI. And there is again, a piece of research which is directly associated with this at the University of Michigan, where Prof. Ronald Lippett is working with a new system of taking out not only mentally retarded children, but gifted children in the sixth grade, to work almost as teachers with children of the same type of the fourth grade. These children in the fourth grade work with children in the second grade. This is called cross-grade teaching. The benefits are not only to the children who are helped but also to the children who do the helping because they do learn more about some of their own specific problems, and work better with them.

Mr. FOGARTY. Who is heading this project in Illinois?

Mr. IANNI. Professor Goldstein.

Mr. FOGARTY. And who is heading it at Stanford?

Mr. IANNI. The one at Stanford is with Prof. Patrick Suppes.

Mr. FOGARTY. They talk about another research project on the advisability of placing retarded children in the regular classrooms. And the result of that study would show that they did much better when they were in a special class for the retarded. Do you agree with that?

Dr. MASLAND. I would hesitate to comment without knowing more of the details.

There is one theory which says that the brain-injured child—the child with a neurosensory defect—is more effectively trained if extraneous stimuli are excluded so that he can focus his attention on one single object.

I believe there is still a difference of opinion as to how broadly this concept really applies.

Mr. FOGARTY. Well, they have been studying it for 3 years, now.

Dr. MASLAND. Yes.

TREATING MULTIPLE HANDICAPPED CHILDREN

Mr. FOGARTY. What about the retarded child that is also deaf or blind?

Dr. MASLAND. They are very difficult.

Mr. FOGARTY. You do not have anything for the deaf retarded child, do you?

Dr. MASLAND. Very little. There is a group who are blind and retarded. Many of the children who had retrolental fibroplasia suffer both from blindness and from mental retardation.

Fortunately, that population is no longer being increased to any significant degree.

Mr. FOGARTY. It should be going the other way, should it not?

Dr. MASLAND. It is primarily the ones who were affected before we learned to control retrolental fibroplasia and are now growing up that we have to worry with. We do have some investigations with that group of children in order to study the effect of congenital blindness on their development of intellectual capacities, and particularly, to learn what we can about ways of training such children who represent quite unusual and difficult problems. The resources for training them are very limited.

Mr. FOGARTY. What are we going to do for them? Just because they are deaf and blind—

Dr. MASLAND. Well, I think the most important thing we can do is to prevent it.

Mr. FOGARTY. I agree, but we should be doing something for those that are blind and deaf, rather than just providing space for them in some building.

Dr. MASLAND. Yes.

BLINDNESS RESEARCH ACTIVITIES

Mr. FOGARTY. What work are you doing in blindness?

Dr. MASLAND. I reported last year on the treatment, discovered by Dr. Kaufman, of certain forms of infection of the eye. This is proving to be a very valuable measure. There is no question that prompt treatment of this particular form of inflammation of the cornea will now prevent loss of vision.

We are working very hard to obtain more accurate information regarding the magnitude of some of the problems. For example, the one that you mentioned. Nobody really knows how many children there are who have both blindness and mental retardation or how many have both blindness and deafness.

Mr. FOGARTY. Why should we not know?

Dr. MASLAND. We are trying to find out. We are developing now a model reporting study with 17 different States cooperating to obtain uniform statistics on blindness.

In most States, blindness is a reportable disease, but the reporting systems have differed from one State to another and their degrees of accuracy vary. A uniform system is being developed with a central data-collection arrangement, so that we will soon have available more uniform statistics on blindness.

We need this information, for example, in connection with visual aids. We have been consulting with people who are working on the development of aids for blindness who need to know how many people will need their services.

We are getting some very valuable new information, also, regarding the basic mechanisms of vision.

Mr. FOGARTY. We have the National Health Statistics coming before us very soon.

Dr. MASLAND. Yes.

Mr. FOGARTY. What are they doing to help you in this area?

Dr. MASLAND. We are working with them in the development of some studies to determine the actual nature of the blindness which is reported. The National Health Survey has relied very heavily on questionnaires, which ask such questions as, "Is there someone in your house who is not able to read the newspaper?" You cannot go much further than this with an interviewer. However, we are developing with them, some special investigations, in which followup examinations will be made of individuals who are so reported in an effort to determine exactly the nature of the blindness involved.

RESEARCH GRANTS PROGRAM LEVEL

Mr. FOGARTY. As in the other Institutes, most of your increase is in research grants, and we find the same pattern here, as in all the others, with the exception of mental health. That program is leveling off. This is another very conservative budget. All of this increase is to fund the continuing program; nothing to pay for an increase in the number of new grants. The new grants for 1963 and 1964 are remaining the same.

Dr. MASLAND. That is right. The number of new grants which would be funded under the new budget is the same as we funded this year. I think the figure for the new grants is \$9,415,000.

PARKINSON'S DISEASE

Mr. FOGARTY. What are you doing in Parkinson's disease? You mentioned something in your opening statement.

Dr. MASLAND. The most dramatic development in Parkinsonism is the surgical treatment of tremor. In certain selected instances of Parkinsonism, destruction of portions of the brain by newly developed surgical means will alleviate tremor.

A person with Parkinsonism suffers from three different disabilities. They have rigidity, uncontrolled tremor, and a loss of associated movement. They do not smile in a natural way. When they walk, they do not swing their arms naturally. Movements which take place in most people automatically, are lost.

The surgical treatment can relieve the tremor and rigidity but, unfortunately, it does not have very much effect on loss of movement. It is a most important step, especially since it is rendering increasing knowledge of the basic mechanisms of this disease.

Another important advance has come from the study of drugs which are capable of producing Parkinson's disease. If you give too large a dose of chlorpromazine or certain other tranquilizers, the person develops symptoms which look very much like Parkinsonism. Fortunately, in most instances, it is reversible by withdrawal of the drugs. This gives us a clue that there may be a chemical basis for the disease.

Further evidences of this are appearing from studies of the urine. Scientists are reporting chemical disturbances in the urine of patients with Parkinsonism, which seems to relate to the activity of parts of the nervous system which are not functioning properly. So it looks very much as though some form of Parkinsonism may be the re-

sult of a chemical derangement of the nervous system. It is a very hopeful sign because if we can find out what the chemical abnormality is, we will have a key for prevention. At the moment, all we can do is alleviate it.

Mr. FOGARTY. Have you been able to induce this in monkeys?

Dr. MASLAND. Yes, we have had monkeys with Parkinsonism induced by drugs. It has not been possible to produce Parkinsonism by surgical means, possibly because the pathology of Parkinsonism is spread diffusely through the brain.

Another approach to the cause of Parkinsonism, which I mentioned last year, is to look for a virus. We know some forms of Parkinsonism are the result of encephalitis. We have established a facility at Patuxent, in collaboration with the Fish and Wildlife Service, where we will inoculate animals with material from patients suffering from chronic diseases of the nervous system, and look for viruses, especially slowly developing viruses.

There is a report from Russia—which I think is open to serious question but certainly must be investigated—that they have found a virus in amyotrophic lateral sclerosis, another chronic disease of the nervous system.

Mr. FOGARTY. That is one of the worst, is it not?

Dr. MASLAND. That is one of the most devastating, yes.

The statement by the Russians is that they injected material from a patient dying of this disease into an animal. It took 3 or 4 years before the disease developed in the animal. This is the type of study that we are proposing to do at Patuxent, where we can have an animal in isolation for a long period of time. We want to look for viruses in amyotrophic lateral sclerosis, multiple sclerosis, and Parkinson's disease, among others.

SPECIAL REPORT

Mr. FOGARTY. We will place your special report on parkinsonism in the record.

(The report referred to follows:)

THE PROBLEM

A major problem of disability in the United States is parkinsonism or Parkinson's disease, sometimes called by its older name, shaking palsy. Two handicapping symptoms are a progressive and highly disabling muscular rigidity and a distressing and uncontrollable trembling or tremor. The tremor almost always disappears during sleep. A third basic component of the disorder results from disturbances of "automatic movements" and may manifest itself in abnormal gait, a tendency to run in order to avoid falling backward, a lack of the usual "righting" efforts when a fall backward or to the side threatens, and loss of automatic movements such as arm swinging. A masklike face often appears, due to loss of normal muscle movements in the face, and many other symptoms complicate the lives of some patients.

Extreme variability marks the rate of development of this disability. Some patients continue on their jobs for many years, with a limited tremor and stiffness on one side only. Others become wheelchair or bed patients requiring total care within months of onset of Parkinson's disease.

It has been difficult to identify the extent of the prevalence of parkinsonism. Although no definitive national figures exist, several surveys indicate 300,000 to 500,000 cases in the United States. A survey of one community by Institute epidemiologists was adjusted for the U.S. population to predict that from 25,000 to 43,000 persons will be newly afflicted each year. One scientist suggested that the majority of present cases stem from the combined influenza and encephalitis

epidemics of 1918 and the 1920's, and that the total number of cases of parkinsonism will therefore decrease. A contrary view is that the increase in total numbers of older persons will be accompanied by an increase in the total cases of parkinsonism unless a cause and its preventive are found. If the latter view is correct, parkinsonism can be expected to continue to increase until its causes have been discovered and can be prevented, or a successful treatment for the majority of cases is developed.

NATURE OF THE DEFECT

For many years, it has been known that the symptoms of parkinsonism are a manifestation of injury or disease of certain portions of the brain and nervous system. The focal point for the disturbance lies in the basal ganglia, aggregations of nerve cells deep within the brain substance. Their activity is essential to the maintenance of tone and body movement.

Only recently, however, have we begun to obtain an accurate picture of the essential nature of the defect. A baffling enigma handicapping past research has been our inability to reproduce signs of parkinsonism by the means of experimental injury to the basal ganglia in animals. Various types of paralyses have been produced in animals, but none has had the true picture of parkinsonism as it is observed in human patients.

It appears that the signs and symptoms of parkinsonism result from a selective injury or dysfunction of a system of nerve cells. It would require selective destruction of this system to reproduce the clinical picture in animals and this is almost impossible to achieve by surgical means. However, animal research in parkinsonism now is being conducted by means of chemical or medical substances with powerful effects at known sites in the nervous system. In some animal research, chemicals are proving more useful than surgery in producing an experimental animal with signs resembling parkinsonism of man.

Furthermore, in research requiring stimulation of a nerve, drugs are often used instead of an electrode. This advance in use of drugs to replace either surgery or electrical stimulation in research can be applied not only to animals but also to man.

There are now known to be two parallel and opposing circuits of nerves from the brain to the muscles of the extremities of the body. A delicate balance between these two systems is required for proper muscle tone and body movement. One of these systems, the alpha motor system or alpha efferent system, extends from the surface of the brain, through the basal ganglia, and directly to the muscle. It is the primary pathway for causing muscle movements. Its activity is accomplished through a chemical transmitter of messages, acetylcholine.

A newly discovered parallel system from the brain to the muscles is called the gamma motor system or gamma efferent system. It also extends throughout the nervous system. Its activity is a more complicated one, involving a regulatory function for muscle movement as contrasted with the direct production of a muscle movement of the alpha motor system.

The gamma system also depends heavily upon the mediation of chemical transmitter compounds, the catechol amines, including serotonin.

In individuals suffering from parkinsonism, it now appears that the alpha system is relatively overactive, whereas the gamma system is suppressed or injured.

A major clue to this discovery came from the investigation of tranquilizing drugs. Reserpine and the phenothiazine derivatives, if given in large doses over significant periods of time, will produce a picture resembling parkinsonism. Although this may occur in about 15 percent of treated patients, fortunately the tremor and other symptoms usually stop when the drug is discontinued.

These tranquilizing agents are known to affect the gamma system of nerves for muscular control by blocking the chemical transmitter substances essential for the system's functioning. This evidence has demonstrated that parkinsonism occurs in this instance due to inactivation of the gamma motor pathways, and overactivity of the alpha motor pathways.

Suggestive of additional evidence of a fundamental derangement of these nerve circuits in parkinsonism is the preliminary finding of an abnormally high excretion level of substances related to the catechol amines exhibited by patients.

NEW APPROACHES TO TREATMENT

Suppression or reduction of the activity of the alpha motor system is the time-honored approach to treatment of parkinsonism. Medical treatment to date has relied primarily upon the use of blocking agents to reduce the activity of the acetylcholine transmitter system, and thus to reduce the influence of the alpha motor pathways.

The advances in our understanding of the normal and abnormal functions of the alpha and gamma systems have prompted a new approach toward the treatment of parkinsonism, that of increasing the activity of the gamma motor system with appropriate medicines. While this approach appears logical, to date it has not been successful, and more research is indicated.

Although a great variety of drugs affecting the alpha system are now available, treatment must be individualized. Through such selective treatment, a 20-30-percent decrease in tremor and rigidity in parkinsonism patients may be accomplished. Investigators are continuing to explore new drugs influencing both motor systems.

The most successful new development in treatment of parkinsonism has been through surgery, which has relieved tremor and rigidity in 70- to 80-percent of selected cases. Such surgery has not restored lost movements nor cured the disease.

The purpose of the surgical approach is to destroy a portion of the alpha motor system, thus reducing its activity and restoring a more normal balance between the alpha and gamma systems.

The development of techniques for the accurate localization of areas deep within the brain, and often less than one centimeter in diameter, is a tribute to the skill and ingenuity of the neurosurgeons who have devoted themselves to making this operation safe and effective.

The earliest surgical approach employed a simple cutting instrument; a later approach used the injection of chemical agents; and within the past year or so local freezing of the crucial area of the nervous system has produced partial relief in patients with parkinsonism. An interesting recent development has been the use of high-frequency sound waves through which the nuclei deep within the brain may be selectively destroyed through a focused sound "beam" without the necessity of cutting the brain.

MAIN OBJECTIVE—DISCOVERY OF CAUSE AND PREVENTION

Unfortunately, the above measures are all palliative. Our primary objective must be the discovery of the cause and prevention of this disabling disorder. There are two main avenues of approach.

The first seeks to discover some chemical disturbance in the body or in the environment which may cause the symptoms by selectively poisoning the cells of the gamma motor nerve system—structures which clearly have a unique chemical characteristic. It has long been known, for example, that the ingestion of manganese will selectively destroy these structures and produce a picture resembling parkinsonism.

The second employs epidemiological investigation. For the past 5 years the Institute has had an active investigation of a native population with an incredibly high frequency of parkinsonism on the island of Guam. Our most recent figures indicate that 7 percent of this population are afflicted with a severe form of rapidly progressive parkinsonism—in this instance associated with dementia.

An intensive field investigation of this unique situation is now underway. Pathological examinations of the brains of patients who died from this disease are being conducted to look for abnormalities of the enzyme structure. Epidemiological studies are attempting to find environmental factors which may be influencing the incidence in the population on Guam.

Some genetic susceptibility to parkinsonism probably exists. The chemical structure of the nervous system in some individuals may be more susceptible to injury than others. Evidence in support of this thesis has been derived from the study of the relatives of individuals who have developed a parkinsonlike picture while under treatment with tranquilizing drugs for psychiatric disturbances. The incidence of parkinsonism among the relatives of patients who developed tremor was observed to be significantly greater than the incidence among the relatives of a control group of psychiatric patients who did not develop this symptom when given tranquilizing agents.

The cells of the basal ganglia and the gamma motor nerve system have a specific affinity for selective destruction by certain viruses. A unique form of parkinsonism is that spoken of as "chronic epidemic encephalitis." The influenza epidemic of 1918 to 1920 was followed by an epidemic of encephalitis characterized by severe injury to the basal ganglia.

There is a possibility that the virus may still exist in attenuated form in the population, and that occasional cases of mild encephalitis are still being followed by the development of a Parkinson picture. For this reason the search for a viral cause of this disease is an important part of the total program.

This year, the Institute, in cooperation with the Fish and Wildlife Service, U.S. Department of the Interior, has established a research laboratory to search for viruses in chronic diseases of the nervous system. In view of the long latency of this disability, animals inoculated with suspected material must be kept for long periods of observation. The resources of the Fish and Wildlife Service facility at Patuxent, Md., are ideal for the long-term isolation of such animals. The small facility being constructed will be used to seek the isolation of viruses from patients suffering from chronic epidemic encephalitis and related chronic diseases of the nervous system.

Research in parkinsonism already has brought advances in treatment, and should eventually lead to understanding of causes and a mode of prevention.

MULTIPLE SCLEROSIS

Mr. FOGARTY. Now that you mentioned sclerosis, are we making any headway in multiple sclerosis?

Dr. MASLAND. Yes. Some of the testimony in regard to the field of allergy relates to this, in that multiple sclerosis may be another "autoimmune" disease.

The destruction of the nervous system, which takes place in multiple sclerosis, may occur when the body develops an immunity against nervous tissue, and the antibodies in the body proceed to attack its own nervous system. This is one of the theories of multiple sclerosis.

There is more supporting evidence for this, this year, in that antibodies against neural tissue are being found in the circulating blood of patients with multiple sclerosis.

We are attacking it from a slightly different point of view from that which was previously reported. Metholtrexate, the drug which blocks certain immune responses, has been tested in experimental animals for effectiveness against the autoimmune response. Efforts also are being made to find a means of blocking the reaction between the antibody and the neural tissue.

MUSCULAR DYSTROPHY

Mr. FOGARTY. It has been reported some progress has been made in determining the metabolic defect in muscular dystrophy.

Dr. MASLAND. Yes. There are a number of people who are working in an effort to determine the basic nature of metabolic defects in muscular dystrophy. Recently, a meeting of a number of scientists was held to review the work in this research area, and I believe further investigations will be carried forward along these lines.

There are a number of different diseases which produce a picture of muscular dystrophy, and one of our major efforts has been to separate these diseases and to determine the basic defect in each. We now have distinguished three or four diseases which were not recognized as recently as 4 years ago, and had been grouped with other forms of

muscular dystrophy. In each, there is a specific biochemical defect present. Of course, the separations of these disorders and the identification of the biochemical defects are essential steps toward finding a way of reversing the defects.

SPECIAL REPORT ON NEUROMUSCULAR DISORDERS

Mr. FOGARTY. We will place your special report on neuromuscular disorders in the record.

(The report follows:)

THE PROBLEM

Muscular and neuromuscular disorders present a variety of symptoms. In one, the muscle may not be able to contract effectively; in another, the muscle may contract at the slightest stimulus but may not be able to relax normally. In still other diseases, the muscle tissue may waste away as a result of damage to nerves serving the muscle or to a defect in the muscle tissue itself.

Some forms of neuromuscular disease appear in the first years of life; some during puberty; others do not appear until adult life. The clinical course of the disease may be slow and steady or, in some cases, interrupted by long periods of remission.

It is understandable that such a complex problem is difficult to assess in terms of money spent, man-hours lost, and the suffering and hardship of the afflicted and their families. In recent years, the prevalence of muscular and neuromuscular disorders, as a group, has been estimated as 200,000 partially disabled and 50,000 completely disabled, and the cost of the care of patients as \$150 million.

Treatment and diagnosis of neuromuscular disorders require many techniques and skills, and demand the research contributions of many fields including biochemistry, electrophysiology, and electron microscopy.

The Institute's grants program reflects this need for a broad base of research. A sampling of grant-supported projects shows research ranging from basic embryological studies of neuromuscular systems and genetic models of neuromuscular disease to clinical studies and evaluations of therapy. These samples indicate the diversity of attack necessary to reach the objective of complete understanding of the processes that give rise to neuromuscular diseases and of finding a completely effective treatment or preventive measure.

Last March, the Institute supported a conference sponsored by the New York Academy of Sciences on "Structure and Function of Biologically Active Peptides." Peptides are basic structural units of proteins and are involved in a variety of reactions related to protein metabolism. The role of these compounds is especially important in relation to neuromuscular disorders in which muscle deterioration is predominant.

The Institute also supported a symposium in June sponsored by the World Federation of Neurology, entitled "Enzymatic Activity of the Central Nervous System." This symposium covered a wide range of topics—many of which are important to the understanding of the role of enzymes in the neuromuscular system.

The results of a previous symposium on "Muscle Receptors" were published last year. This book brings together much of the current knowledge on how muscle is activated. This basic knowledge is important in understanding neuromuscular disease.

Neuromuscular disorders may be caused by a primary disturbance anywhere in the neuromuscular system, from the brain to the muscle. The Neurology Institute supports and conducts research that covers the wide range of possible causes. The most prevalent forms of neuromuscular disease are myasthenia gravis and muscular dystrophy and research in these two has offered the most promise in recent years.

MYASTHENIA GRAVIS

Myasthenia gravis is a form of muscle disorder characterized by recurrent weakness of certain muscles, but without obvious atrophy or other gross anatomical defect. The weakness is caused by a failure of transmission of the nerve impulse to the muscle fiber which it should activate; this transmission depends upon the liberation by the nerve ending of a chemical which acts upon the muscle and causes it to contract. In myasthenia gravis, the chemical (acetylcholine) is

liberated but fails to act. The nature of this blocking of its action remains unknown.

But, important recent discoveries suggest that disturbances of the body's immune mechanisms may be responsible. This possibility has been further strengthened this year by the discovery that the thymus gland plays a key role in immunological development.

Antibodies may be produced by the cells liberated from the thymus. Generally the antibodies serve to protect the body against disease by reacting against specific foreign substances (antigens) such as germs or foreign proteins. In some rare instances the antibodies may react against normal body tissue to cause what are called autoimmune diseases.

Myasthenia gravis may be an autoimmune response of muscle, in which an antibody is formed to a protein usually found at the neuromuscular junction. The antibody prevents transmission of nerve impulses at the neuromuscular junction by reacting with the protein at the neuromuscular junction. Studies that support this theory and indicate how the thymus may be involved are discussed below.

Neonatal myasthenia gravis is a unique condition in which the child of a mother with myasthenia has myasthenic symptoms for an average period of 3 weeks. The infant's myasthenia is uniformly transient and does not correlate well with severity or duration of the maternal disease. This suggests that there is a substance in the mother's blood that crosses the placenta to cause these transient symptoms in the infant.

It has long been known that tumors of the thymus frequently occur in myasthenia patients and that removal of the tumor may bring improvement in some cases. In some instances the detection of the tumor preceded the onset of myasthenia by several years. Also, in some instances of thymus tumor, there are groups of cells which are similar to cell groups seen in experimental autoimmune disease. The thymus abnormalities are probably not the primary cause but rather manifestations of some unknown underlying defect.

More recently investigations have shown lesions in the thymus of the patient with myasthenia gravis that are similar to those produced experimentally by direct injection of antigen into the gland.

This accumulated evidence indicates that some defect or injury to the thymus may cause antibodies to be produced which react with a protein found at the neuromuscular junction to produce the symptoms of myasthenia.

These studies provide an additional rationale for treatment with adrenocorticotrophic hormone (ACTH), a drug which modifies the immune reactions of the body and has been used with varying success in certain forms of myasthenia gravis. However, carefully controlled clinical testing is necessary to evaluate therapy in a disease, such as myasthenia, that progresses at different rates, with frequent remissions, and is influenced by a variety of factors affecting the patient.

Currently the Institute is beginning a collaborative study to evaluate the effectiveness of ACTH in treating an ocular type of myasthenia. Six hospitals in the eastern United States will cooperate in clinical trials with a relatively large group of patients.

The evidence that myasthenia gravis may be a unique type of response to some immunologic abnormality, as yet unknown, and the growing indication that the thymus plays an immunologic role which may be controlled by hormones together with the well-established thymic abnormality in this disease, provide substantial direction for future research.

MUSCULAR DYSTROPHY

While myasthenia gravis is a disorder of the neuromuscular junction, muscular dystrophy includes several conditions in which the muscle tissue wastes away. This loss of tissue is almost always progressive and in the late stages of the disease the greater part of the voluntary muscles may be replaced by connective tissue and fat. When we consider that the voluntary muscles of the normal individual account for almost half the total body weight and contain a large percentage of all the body proteins, we appreciate how important the knowledge of protein synthesis and metabolism is to the problem of muscular dystrophy.

While the common denominator of the muscular dystrophies is the loss of muscle tissue, recent studies have shown that there are several types with different characteristics. In past years scientists at the Neurology Institute

have identified some of these disease entities which were previously grouped under the general category of muscular dystrophy. In one, central core disease, for example, they found an abnormal biochemical core of material in the muscle fibers that is responsible for the muscle weakness. In another disorder, McArdle's disease of muscle, they found that the disorder is due to the absence of an enzyme, phosphorylase.

Last year Neurology Institute scientists studied three other heretofore undescribed forms of muscular dystrophy. The first is tentatively called central core disease, type II. The muscle fibers in this disorder have an abnormal central region superficially like the original central core disease but biochemical analysis has revealed a different basic defect. The recognition of this new form is especially important because it has a much more favorable prognosis than the usual type of childhood dystrophy which it mimics clinically.

Another form of dystrophy has been called Nemaline Myopathy. It is characterized by abnormal rod-shaped structures in the muscle fibers which appear to be altered contractile protein that has partially crystallized. The chemical abnormality permitting this abnormal crystallization is being sought.

The third new type of muscle disease appears to be a muscular dystrophy of late onset, beginning after the age of 45. In this particular example of late onset dystrophy, a specific biochemical defect has been found to be the complete absence of the essential enzyme phosphorylase, similar to McArdle's disease in which symptoms begin in childhood.

These studies reflect the work being done in many laboratories in recent years that have further clarified the biochemical defect in muscular dystrophy. Accurate knowledge of the essential biochemical defect of this disorder is probably an essential prerequisite to the development of an effective treatment.

Several investigations have been based on the theory that muscular dystrophy is linked to the abnormal metabolism of high energy phosphates—compounds involved in the production of energy for synthesis of proteins and muscle contraction. Of particular importance are the enzymes that control the metabolism of these compounds.

Early diagnosis, by measuring increase in serum levels of several of these enzymes that accompany the wasting of muscle fibers, has made it possible to analyze in detail the early pathological events that transpire in dystrophic muscle. Significant alterations in the muscle occur before earliest signs of clinical weakness. These alterations seem to involve most of the muscle fibers with a blurring or total disorganization of their internal structure—it may be that such fibers are incapable of functional contraction. In the early stages there is evidence of regenerative and reparative efforts which retard the appearance of the clinical weakness but this capacity diminishes as the disease progresses.

In previous years grantees have shown that the proliferating connective tissue of the affected human dystrophic muscle is rich in some of the enzymes and compounds associated with high energy phosphates. In studies of the process by which rat muscle atrophies, they found much the same situation and conclude that these substances are part of the reaction of the atrophying muscle system in an attempt to facilitate the passage of glucose, amino acids, and other compounds to the damaged muscle. They found that certain nucleotides increased this process and, while the nucleotides did not prevent the irreversible loss of muscle substance, they were generally beneficial in the attempted rebuilding process.

In the past year scientists have initiated several new approaches to therapy based on new findings or development of new drugs. In one series of treatments begun last year, the investigator used a new anabolic steroid, a drug that enhances the building of muscle tissue. The muscular mass of an individual reflects the balance between the processes that break down the muscle tissue and those that build new muscle. In a normal state of health these processes are in balance; in muscular dystrophy, breakdown exceeds regrowth. We do not yet know whether the fault is the limitation of the one process or the acceleration of the other, but it is apparent that breakdown does not keep pace with the rebuilding process.

More than 25 years ago the male sex hormone, testosterone, was shown to have a powerful rebuilding action. Many children and adults with MD were given testosterone and its derivatives. The hormonal effects on sexual characteristics were pronounced and often distressing and while a general feeling of well-being was noted, no significant effect on the course of MD could be shown.

Recently an investigator reported some observation on a series of patients receiving a new steroid (1-methyl- Δ^4 -androstenedione) which may have fewer side effects than steroids used in earlier treatment. He noted increased muscle strength in most of his patients and a general feeling of well-being. The drug does not stop the progress of the disease but apparently only slows it down while giving some comfort to the patients. It is too early in the study and there are too few patients to assess the long-term effects of the drug.

A grantee has used a nucleotide (procaine-3-adenylate) to treat a small group of patients. In from 1 to 5 years of treatment, these patients apparently had no further muscular deterioration. They had increased muscular strength and a lowered excretion of creatine. This same nucleotide seems to decrease the rate of degeneration of denervated muscle in rats.

In both these instances, the studies to date have not supported original hopes regarding the effectiveness of these drugs. These studies do emphasize the complexity of the problem and indicate the directions which research is taking in this field.

PROSPECTS FOR THE FUTURE

In any discussion of disease, the rapidly developing areas of genetics has a special importance. We already know that muscular dystrophy is often hereditary. We also know that certain factors important to the production of enzymes are inherited. There is the possibility that the enzyme, phosphorylase, for example, may be absent because of a genetic defect. There is also the possibility of a defect in metabolism in which a normally nontoxic substance accumulates to harmful concentrations as in phenylketonuria which is associated with serious abnormalities in the nervous system.

Studies of the nucleic acids, DNA and RNA, offer great promise. Inasmuch as the nucleic acids are primarily responsible for the construction of muscle protein, a defect in RNA or DNA structure of configuration could conceivably result in altered or dystrophic muscle.

It is apparent that the theoretical considerations of genetic and enzyme actions could be of the greatest practical value in the management of muscular dystrophy and other neuromuscular diseases. Knowledge of the exact nature of the defect in an enzyme reaction would suggest the type of procedure that could compensate for the defect.

In our present state of knowledge, our understanding of many muscle diseases is still rudimentary. The Institute has developed a coordinated approach to these problems using the anatomic, physiologic, pharmacologic, genetic, and immunologic knowledge now available, with the assurance that these efforts will hasten the rapid development of the information essential to the discovery of the cause and cure of these diseases.

CEREBROVASCULAR DISEASE

Mr. FOGARTY. What are you doing in the field of cerebrovascular disease?

Dr. MASLAND. As you know, we are collaborating very closely with the Heart Institute in this area since it relates to the program interests of each Institute. The Heart Institute is concerned, primarily, with the mechanisms of arteriosclerosis—a process of injury of the blood vessels. Our concern relates more directly to the impact of this to the nervous system and the manifestation of strokes.

We have established a joint committee whose concern is to maintain an overview of this field of cerebrovascular diseases and strokes. This group has been very active in reviewing the status of the field. They prepared a bibliography of strokes which has been circulated quite widely. At regular intervals, the literature is reviewed and reports and supplemental bibliographies circulated around the country so that in every medical school there will be available up-to-date knowledge of the status of this field.

We are working on the problem of the precise diagnosis of cerebrovascular disease. Of particular importance is our program in neuro-

radiology. We are training people in the techniques whereby the blood vessels of the brain can be demonstrated by the injection of contrast media. By these methods, it is possible to get beautiful pictures of the blood vessels of the brain which show great detail. This permits you to localize with great accuracy the site of any arteriosclerotic process.

We have a cooperative project with 17 different institutions studying cerebral aneurysms. To date, they have had under investigation over 4,000 cases of aneurysm in the brain; that is, the vascular dilation of the artery of the brain. They have done some preliminary studies and are in a position to define for the surgeon much more accurately which type of aneurysm would benefit by surgery. Now they are undertaking a control study to determine the best of several methods of treatment. In this study aneurysms are being treated by different techniques; some by surgery, some by bed rest, and others by decreasing the blood pressure. Over a period of time investigators will compare the results of these three different methods of treatment to find out which offers the best prospect for the patients.

We have an extensive program for the study of the epidemiological aspect of vascular disease. We have three different projects, international in scope, which are comparing diseases of the blood vessel of the brain in different countries.

Mr. FOGARTY. Which ones?

Dr. MASLAND. There are projects in Italy, Sweden, Belgium, Japan, and in several countries in South America.

Mr. FOGARTY. Where is the one in Italy?

Dr. MASLAND. In Italy, it is—

Mr. FOGARTY. Turin?

Dr. MASLAND. Yes. There is a very good pathologist there.

SPECIAL REPORT

Mr. FOGARTY. We will place your special report on cerebrovascular disorders in the record.

(The report follows:)

THE PROBLEM

One out of every nine Americans dies of cerebrovascular disease, and the number of persons suffering from this condition continues to rise. Cerebrovascular disease, or stroke, stands third as cause of deaths and a leading factor of chronic disability in the United States.

Cerebrovascular disease includes those disorders in which one or more of the blood vessels supplying the brain are involved. This includes the blood vessels inside the head as well as those in the neck and upper chest. The most common manifestation is stroke. This usually involves some type of paralysis and a variety of other neurological signs and symptoms.

The majority of strokes are caused by three basic processes: (1) thrombosis—the formation, development or presence of a blood clot which remains at its point of formation in a blood vessel; (2) embolism—the sudden blocking of a blood vessel by a blood clot, carried by the blood from a larger to a smaller vessel which it obstructs; (3) hemorrhage—the rupturing of a blood vessel so that blood leaks into surrounding tissue.

The importance of an adequate blood supply is emphasized by the fact that, though the brain comprises but 2 percent of the total body weight, it normally utilizes 20 percent of the total oxygen supply. Brain tissue cannot store oxygen and is dependent from minute-to-minute on an adequate flow of blood. When nervous tissue is deprived of oxygen for more than a few minutes, the cells are irreversibly injured.

Cerebrovascular disease is generally considered a disease of older people. Accidents may occur at any age, but peak incidence for cerebral thrombosis is from 50 to 70 years; and for cerebral hemorrhage, from 40 to 70 years. Cerebral thrombosis is the most common cause of strokes (approximately 60 percent); hemorrhage and embolism cause about 20 percent each.

The most outstanding cause of cerebrovascular disease is atherosclerosis which slows or blocks the flow of blood through narrowing or obstruction of one or more arteries. Patients with high blood pressure show a considerable increase in the severity and frequency of vascular diseases of the brain. Among other causes are congenital defects in artery walls that result in aneurysms, and abnormalities in the blood clotting mechanism which facilitate clot formation.

APPROACHES

The National Institute of Neurological Diseases and Blindness is concerned with the problem of cerebrovascular disease because of the neurological disturbances that result. The blood vessels of the brain, though, are part of the general circulatory system in which the heart is the driving force. Often heart or general vascular disease affects the brain first because of its sensitivity to inadequate blood supply. Many of the problems already mentioned—such as atherosclerosis, hypertension, and thrombosis—thus are problems that relate closely to programs being developed by the National Heart Institute.

In recognition of the common problem, the two Institutes are providing impetus and support for a worldwide attack on cerebrovascular disease. This support has taken a number of forms and the Institutes with their advisory councils, continue to appraise new techniques and approaches to solve the many problems of cerebrovascular disease.

Intramural research related to cerebrovascular disorders is being conducted by staff members of both Institutes in the NIH Clinical Center at Bethesda. Simultaneously, the extramural programs of both Institutes have awarded research grants to several hundred scientists in this country and throughout the world.

Cooperative and collaborative studies are enabling leading scientists in widely separated locations to concentrate on specific aspects of cerebrovascular disease. These projects take advantage of highly trained scientists who are not apt to be found at one institution. Also, much larger patient populations are available in such studies. Through these projects, participating scientists are performing similar research in various medical centers and the results are compared and evaluated in a common analysis center.

In one of these cooperative studies developed by the Institute of Neurology, 17 institutions are evaluating the 4 most common medical and surgical treatments of aneurysms. Another neurology cooperative study of anticoagulant therapy, begun several years ago, is now completing its final phase and the results are being prepared for publication.

A cooperative epidemiological study is also being supported by the Neurology Institute under the auspices of the World Federation of Neurology. Scientists from several nations, including Italy, Poland, Norway, Peru, Mexico, England, and the United States, are either participating in the study or are conducting independent parallel studies.

The objective of the World Federation of Neurology study is to establish correlations among degenerative changes in the cerebral vessels found at autopsy, environmental conditions, and other factors such as sex, age, race, culture, diet, and geographic influences.

Three separate but parallel collaborative studies on the pathology of the disease have developed in conjunction with the main epidemiological investigation. These parallel studies were initiated in response to the need for more detailed information about the basic pathology of cerebrovascular disease. They are a study of the large vessel at the base of the brain, a study of the severity of arteriosclerotic changes in the disease, and a study of the structure of the wall of the blood vessel.

A goal of part of this study is to clarify the relationship between serum lipid levels and cerebral atherosclerosis. This relation is confusing because the Japanese and the South African Bantu, for example, have low serum lipid levels, but disease of the cerebral vessels is common and coronary artery disease is infrequent. This suggests that environmental factors may be an important cause of cerebrovascular disease. The study of a variety of populations, with

some common and some different factors, may reveal a common causative factor in this disease.

A special type of cooperative study is the "paired" grants program in which investigators from an American and a foreign institution collaborate in an area of common interest. These cooperative studies provide greater patient populations for study, while utilizing specialized laboratory techniques and specially trained personnel not otherwise available in a single laboratory.

The Neurology Institute's first paired grant in cerebrovascular disease was awarded in 1962 to the University of Minnesota and the University of Kyushu in Japan. In this program both institutions are undertaking a comprehensive clinical and pathological study of cerebrovascular disease, using identical techniques. A comparison will be made between the American and Japanese populations being studied.

A recent development in research programs has established program projects and clinical centers for cerebrovascular disease. Groups of investigators in one institution who have been trained in different medical and surgical specialties and disciplines are now working together, applying their combined talents and efforts toward solving the problems related to cerebrovascular disease.

Under this program an institution receives support for physical resources, research services (such as research bed costs, laboratory needs for research patients, and ancillary care), and the overall research costs, including salaries for research personnel. Research in these clinical centers typically involves exacting observations on patients, such as physiological and metabolic determinations. These observations are carried out in regular hospital bed units, in outpatient facilities, or in special bed units reserved exclusively for the use of study patients. The Institute of Neurology is supporting three integrated research centers devoted to cerebrovascular disease, located at the University of Minnesota, Minneapolis; Wayne State University, Detroit; and Cornell University, New York City.

DIAGNOSIS

Clinical manifestations of cerebrovascular disorders may occasionally be quite characteristic, allowing diagnosis of location and primary cause. More often, however, it is difficult to locate the precise area of involvement in the nervous system and to identify the underlying and precipitating causes of disease.

Generally, the diagnosis of cerebrovascular dysfunction begins with a particular neurological manifestation or symptom which usually depends upon the anatomic location of the disorder rather than its nature. Thus, the same signs and symptoms in vascular disorders may occur in other types of disturbance involving the same cerebral areas. For example, the differentiation between brain tumor and cerebrovascular disease may cause considerable difficulty. Because of these uncertainties, accurate diagnosis now often requires the use of specialized methods of study and their correlation with carefully elicited clinical findings. It is important for the physician to recognize the limitations of various tests in order to improve the reliability of this diagnosis.

The principal problem in cerebrovascular diagnosis is the inability to view the total circulation of the brain directly. The best diagnostic aid presently available for this purpose is angiography. In this technique, a substance that is opaque to X-rays is injected into the blood vessels feeding the brain and then an X-ray picture is taken, thus making it possible to visualize the vascular system of the brain. Although this is considered the best diagnostic aid available, it does have its shortcomings and research is in progress to improve the effectiveness and safety of the technique.

Initial reports on the use of a promising new radiographic contrast agent in cerebral angiography were made by a Heart Institute grantee during the past year. Laboratory and preliminary clinical trials showed that visualization of the major brain arteries was excellent with this contrast medium and side effects were found to be less than anticipated.

A common procedure in angiography is to compress one of the major arteries in the neck to allow a more accurate visualization of the blood vessels of the opposite side of the brain. Studies by a grantee of the Institute of Neurology indicate that routine artery compression during angiography may cause a blood pressure rise in the brain that is potentially dangerous in patients with recent intracranial hemorrhage. They found that the safety of this technique could be improved by applying compression higher on the neck than is usually done

and holding it for a shorter period of time. Blood pressure did not increase as much as with the older technique, yet the diagnostic value of compression was maintained.

Cerebral angiography is not used until some symptoms of neurological disease or disability have already occurred. This emphasizes the need for safer diagnostic procedures that could be applied in routine physical examinations before cerebral damage occurs. Such a procedure would be particularly useful in cases where blood flow in arteries in the neck has been impeded. In some of these instances early medical or surgical treatment might avert damage.

In a study jointly supported by the Neurology and Heart Institutes, the usefulness of auscultation (listening to the sounds) of the major extracranial vessels in the neck, as a means of detecting impeded blood flow, was evaluated in 50 patients with cerebrovascular disease. Auscultation of the carotid and vertebral arteries of the neck led to detection of about 50 percent of the cases in which impeded blood flow was demonstrated by angiography.

TREATMENT

The treatment of patients with cerebrovascular diseases depends heavily on the accuracy of the diagnosis. Studies to determine the best use of existing treatment when the condition has been identified continue to be supported by both the Neurology and Heart Institutes.

In a collaborative study supported by the Heart Institute, data from 24 participating research teams is being accumulated that may prove useful to physicians in determining treatment. Patients with symptoms of cerebral arterial insufficiency are being studied by angiography and other diagnostic techniques to determine the importance of blocked blood flow in neck arteries supplying the brain. Those with occluded arteries who are judged likely to benefit from surgery are operated upon to remove or bypass the obstruction to blood flow. It is hoped that the study may result in improved criteria for selecting patients for surgery and for determining the optimum form of treatment.

In another evaluation of existing treatment, a research team supported by the Heart Institute has reviewed its experience with surgical treatment of partially blocked arteries in the neck and upper chest. The summary of the study shows gratifying results in restoring blood flow and relieving the symptoms of insufficient cerebral blood supply. Of 382 patients with neurological disturbances, symptoms were relieved immediately in 85 percent of those patients subject to mild forms of stroke, and in 65 percent of those with more serious, apparently permanent stroke symptoms. Followup observations, ranging from 8 months to 8 years after an operation, showed relief of symptoms had been maintained in 90 percent of the patients with temporary stroke and in 69 percent of those with more serious symptoms.

Blood clots often are responsible for slowing or stopping blood supply to parts of the brain. Reports a few years ago concerning the use of anticoagulants in the management of patients with cerebrovascular disease were encouraging, but more recent studies have questioned the value of these drugs when administered to patients with acute cerebrovascular occlusion. They suggest that anticoagulants offer little as long-term therapy in preventing recurring transient stroke.

The cooperative study on anticoagulants, organized by the Institute of Neurology to evaluate the various uses and the effectiveness of these drugs, is now in its final phase. Data being prepared for publication will demonstrate the relative usefulness of anticoagulants in different types and phases of cerebrovascular disease.

Neurology and Heart Institute grantees also have been studying the effectiveness of fibrinolytic agents. These agents are used to dissolve clots in the blood vessels without adversely affecting other factors in the blood and without producing adverse side effects. Fibrinolytic agents have been used for years to dissolve clots in the arteries of the legs. Now, improved fibrinolytic agents are being used to treat cerebrovascular problems. One neurology grantee has been studying patients with increasing neurological impairment after the onset of stroke. He has been treating them with anticoagulants plus fibrinolysins or anticoagulants alone in a study that promises to provide vital information about the effectiveness of this combined therapy.

In most cases of cerebral embolism, the material that blocks the artery is a fragment from a blood clot somewhere else in the body, usually the heart. Embolism due to fat, tumor cells, or air, also occurs but is very rare.

Because of the widespread use of therapeutic and diagnostic procedures in recent years in which there is the possibility of air entering the circulation, air embolism has increased in importance. In experiments on dogs, it has been shown that less than one milliliter of air can be damaging or fatal when introduced into the arteries of the canine brain. This is contrary to older reports indicating that relatively larger amounts of air or gas in the arteries of the brain are necessary to obtain mortality in dogs. Present investigators conclude that older experimental techniques facilitated the shunting of the embolism into the vessels in the neck before it reached the brain. Neurological signs in dogs are similar to those described in man.

Approximately 25 percent (or 50,000) of the 200,000 deaths from cerebrovascular disease in the United States each year are due to intracranial hemorrhage. Despite surgical intervention, the mortality rate during the acute phases of intracranial hemorrhage has not been reduced greatly during the past decade. Contraindications exclude the majority of acute cases from major surgical treatment. Hence, it is important to assess carefully various forms of medical treatment and conservative surgical treatment.

In the Neurology Institute's cooperative study of aneurysms and acute hemorrhage, 17 institutions are evaluating the 4 most common medical and surgical procedures for treatment of cerebrovascular aneurysms. These pouchlike enlargements, occurring in cerebral arteries, weaken the arterial walls and lead to rupture and, frequently fatal hemorrhage.

At one of the institutions cooperating in this study, the investigators found that the surgical treatment of aneurysms of the middle cerebral arteries had a much lower mortality rate in men than it had in women. Also, the surgical mortality rate was significantly lower in these men than that of a comparable group of men treated medically.

A followup study revealed an anatomical difference in the shape and location of aneurysms in men and women. The aneurysms that form in men are shaped so that they are more easily treated surgically. In women, the aneurysms are less accessible and when they do rupture there is a greater chance of damaging small cortical blood vessels and thus producing brain-tissue damage.

Aneurysms present a particularly difficult problem to neurosurgeons, even when it is possible to carefully locate them. Often they are in a most inaccessible area of the brain and their thin walls are apt to burst at the slightest touch, causing a serious hemorrhage.

Two new surgical procedures for treating aneurysms have been announced in the past year. In one approach, a research team supported by the Institute of Neurology has successfully repaired leaking cerebral aneurysms by surrounding them with a plastic jacket of a rapid-hardening silicone rubber preparation. The silicone is a thick white liquid which becomes firm within a few minutes on the addition of a catalyst. This plastic jacket retains its properties over a wide temperature range and is resistant to moisture and oxidation. After animal experimentation to test the strength of this material and its lack of irritation when in contact with the brain, the silicone was used successfully to repair human aneurysms.

Another new technique for treating cerebral aneurysms has been the development and use of a specially designed compressed air gun. After opening the skull and exposing the aneurysm the neurosurgeon places the gun against the aneurysm. By merely touching the aneurysm with the tip of the gun, a single hair is propelled into the aneurysm. The hair initiates blood clotting within the aneurysm. This operation was first used on a patient in June 1962 with satisfactory obliteration of the aneurysm. To date, the procedure has been used successfully in 11 patients.

As mentioned earlier, high blood pressure appears to be another contributing cause of brain hemorrhage. Drugs to induce a reduction in blood pressure have been used in the control of intracranial bleeding. However, until recently there had been no controlled studies on the prolonged use of medically induced low blood pressure (hypotension) in the treatment of intracranial bleeding. In one Neurology-supported study of 312 patients with acute spontaneous intracranial hemorrhage, half of the patients were given hypotensive drugs to maintain blood pressure at lower levels. Otherwise, all of the patients were given the same conservative treatment. In this long-term study, the group receiving the hypotensive drugs had a higher survival rate than the group that did not. The investigators recommended that patients suffering from primary hypertensive hemorrhage be

treated with hypotensive drugs. This form of therapy is being further evaluated within the cooperative aneurysm study.

A new technique, referred to as hyperbaria, used for victims of tetanus and carbon monoxide poisoning, also appears to have implications in the treatment of cerebrovascular disease, where recent findings are of great practical importance at higher-than-normal pressure, thus saturating the blood and tissue with a greater amount of oxygen than would be possible at normal pressure.

The National Institutes of Health recently awarded a construction grant for an operating room to be built with a hyperbaric chamber. The chamber would be used in research studies of emergency treatment of stroke caused by insufficient blood supply. The extra oxygen added to the blood might forestall permanent damage to brain tissue and give time to correct the defect.

SCIENTIFIC COMMUNICATION

Effective scientific communication is essential in an area of research, such as cerebrovascular disease, where recent findings are of great practical importance to physicians and to other researchers. Several methods for facilitating communication in the cerebrovascular research area are being pursued.

An example, mentioned above, is a product of the Institute's cooperative study of anticoagulants now being prepared for publication. This will serve as a guide for application of anticoagulant therapy in many cases of cerebrovascular disease.

The Neurology and Heart Institutes' Joint Subcommittee on Cerebrovascular Disease is reviewing the present trends of research and establishing communications among researchers in the field. This Subcommittee was responsible for the wide distribution of the Neurology Institute's cerebrovascular study group report on the status of cerebrovascular disease. This report was distributed in 1962 to neurological departments at medical schools throughout the Nation and has received favorable comment from the scientific community. It has become widely used as a technical resource in medical schools and as a reference in research. The subcommittee is planning to publish a revision of the report in 1965 to keep research workers and the medical community aware of the latest research developments in various aspects of this field.

The subcommittee has invited a small number of investigators to participate in a workshop on the research concerning cerebral blood flow problems. The workshop will be held in the summer of 1963 to evaluate various methods of measuring cerebral blood flow. Results of such workshops are published to keep investigators informed of latest developments.

The "Cerebrovascular Bibliography," prepared with the cooperation and assistance of the National Library of Medicine, is providing a continual index of research on cerebrovascular diseases. It is being evaluated as a permanent tool for researchers in cerebrovascular disease. Preliminary reports from the field are favorable.

The Fourth Princeton Conference on Cerebrovascular Disease has been scheduled for January 1964. This conference will be sponsored by the American Neurological Association and the American Heart Association and supported by the Neurology Institute. It will be concerned with the most promising advances in the field since 1961. These will include advances in the study of atherosclerosis, fibrinolysis, anticoagulants, and cerebral blood flow. The conferees also will be discussing various diagnostic techniques and their complications. The transactions of the fourth conference will be distributed by the Joint Subcommittee as were the transactions of the third conference held in 1961.

PROSPECTS FOR THE FUTURE

During the last 5 years, significant advances have been made in diagnosing and treating persons with cerebrovascular disease. However, with our aging population the morbidity and mortality figures for patients with cerebrovascular disease continue to increase.

It is well recognized that most cerebrovascular disease is due to atherosclerosis. A common combination in the development of strokes is atherosclerosis and the tendency of blood to clot at the sclerotic regions in the blood vessels. The better understanding and possible prevention of atherosclerosis should contribute to the control of cerebrovascular disease. Also, increased knowledge of the clotting process and the action of therapeutic agents, such as anticoagulants and fibrinolytics, should increase the success in treatment.

Significant steps have been made in the surgical treatment of diseased blood vessels. The successes, however, have been concerned primarily with repair of the extracranial arteries. Newer surgical procedures must be developed for treating patients with intracranial disorders.

As we develop better forms of surgical and medical treatment, it becomes apparent that some of them might be used before permanent damage to the brain occurs. This has emphasized the need for adequate early detection techniques. Angiography has been extremely helpful in speeding accurate diagnosis. It is one of the most productive tests for diagnosing arterial block, hemorrhage, tumors, and aneurysms. We can expect this technique to become more widely available and, at the same time, its safety and convenience to the patient increased.

Both the Neurology and the Heart Institutes continue to encourage maximum distribution of research results to the medical community through conferences, symposia, workshops, and various publications. New methods to make such information immediately available to large numbers of investigators and practitioners are constantly being sought. As the techniques of electronic data processing become more widely used, the effectiveness of the rapid dissemination of research information should improve.

There continues to be a shortage of qualified neurologists and related scientists. As new techniques are developed, even more specialists will be needed. At the present time, the Neurology Institute is supporting training programs at institutions where nearly 500 graduate physicians are preparing to specialize in neurology, neurosurgery, neuropathology, and neuroradiology. And these specialists of the future are learning the latest procedures relating to diagnosis, prevention, and treatment of cerebrovascular disease.

NEED FOR TRAINING IN NEUROLOGY

Mr. FOGARTY. As I said earlier in the hearings, in talking to some rehabilitation people about the time these hearings started, one example given was that a student may be getting more hours in typhoid fever, than in stroke.

Dr. MASLAND. Yes. This is where I feel that this program to emphasize neurology in every medical school will pay off, because these are the people who are concerned with this group of diseases.

Mr. FOGARTY. Would the recruitment and training of neurologists be facilitated if there could be established in every medical school a training program in this specialty?

Dr. MASLAND. Yes.

Mr. FOGARTY. Would special inducements encourage general practitioners to train as neurologists to help fill this need?

Dr. MASLAND. Yes. I think this would be valuable. We are going to continue to have a shortage of well-qualified neurologists. No matter what we do, there will not be enough. This means, that as an alternative, and I think it is important that it be recognized that this is second best, we must train a lot of other people to fill in as much as possible. This means the use of extension courses, short courses, seminars, and everything that can be done to provide training in neurology for specialists in other fields.

Mr. FOGARTY. What about the training of the general practitioners?

Dr. MASLAND. Yes; this would be a most important measure.

Mr. FOGARTY. It has worked well in mental health.

Dr. MASLAND. That is right.

Mr. FOGARTY. Could it be done in your field?

Dr. MASLAND. It could be done. We would have to provide stipends for the man in training, which might be up to 6 months, but I believe we have to train everyone that we can in this field.

Mr. FOGARTY. Are special measures required to train neurologists in these fields?

Dr. MASLAND. I believe that these people can be trained within the neurological training programs. I should mention, here, our training program in pediatric neurology which is directed primarily toward the problems of the child with emphasis on mental retardation.

Although it is broadly oriented, the pediatric neurology training program is providing essential training related to mental retardation.

TREATMENT OF EPILEPSY

Mr. FOGARTY. You mentioned epilepsy. What are they doing in epilepsy?

Dr. MASLAND. We have a number of studies in progress. Actually, our expenditures now in epilepsy are at the level of about \$3½ million a year. We are getting some interesting data from the collaborative project which show an incidence of epilepsy of about 5 per thousand in that population. This is approximately what we had previously considered the incidence of epilepsy to be. However, this is in a group of people who are leading relatively normal lives and it is an indication of the extent to which the person with epilepsy today, is being integrated into the regular activities of society.

We are working on the fundamental nature of epilepsy. We now know for example, that probably between 7 and 10 percent of the population have had at least one convulsion in the course of their lifetime. In many of these, convulsions occurred only in childhood. A great many children have seizures in childhood and outgrow them.

There was a time when we thought this phenomenon did not exist, but the evidence now indicates that the old fable that a child might outgrow his seizures has considerable support.

From the point of view of treatment, our chief reliance still has to do with the use of anticonvulsive drugs. Each year we have added two or three drugs which are effective in patients not adequately treated with the previously standard drugs.

We have encountered a very unexpected problem in relation to the drug companies. I have approached several of them about more active investigation of anticonvulsants. The response is that the drugs we have now are so effective that the group of people for whom we would be developing a new drug is relatively small. Furthermore, a person taking an anticonvulsant must do so for a long period of time and any new drug that is developed must be nontoxic. Thus the costs of development and the risks involved are so great that the drug companies do not feel it is worth the risk to put a large share of their resources in the development of anticonvulsant drugs.

From the point of view of numbers of patients this may be fine; but from the point of view of the individuals whose seizures are not controlled by the presently available medication, it is not an adequate solution and I believe that it will be necessary for us to be more aggressive in our efforts to develop new anticonvulsant drugs. This may require a contract program or a new approach to getting things moving in this area.

Mr. FOGARTY. I think something should be done.

REGULATIONS REGARDING MILITARY RETIREMENT PAY TO EMPLOYEES

I have just one more question, Doctor.

Do you know anything about a civil service rule that a retired Army officer would have to forfeit his retirement benefits if he took a job with you people?

Mr. KELLY. I might answer that, Mr. Chairman.

It is a complicated rule because there are certain exceptions to it that relate to the Reserves, but basically speaking, the law prohibits a total income from military retirement and from civilian pay that exceeds \$10,000. So that in order to take a position at the professional level, you have to give up the retirement.

Mr. FOGARTY. That does not seem quite fair, does it? I know you people have lost some good men because of that.

Dr. SHANNON. It goes beyond that, Mr. Kelly. If a retired officer comes into employment in another Government agency, before he is employed as a civil servant, he must give up all his benefits that have accrued as a result of military service. He receives no personal benefits from the civil service until after he has been employed for 5 years, at which time he then can pick up and apply prior benefits toward the final civil service retirement. But the critical thing here is that during a period of 5 years he has no coverage. He has completely lost his military coverage, and he has not acquired any permanent civil service coverage.

Mr. DENTON. I thought, Doctor, that was just held in abeyance during that 5-year period.

Dr. SHANNON. No, sir. He has lost it if he dies during the 5-year period. It is held in abeyance in this sense, that when he has permanent civil service retirement rights, then the calculation of those rights of his military service is computed in. You see the point I am trying to make?

Mr. DENTON. That figure runs up in the thousands of dollars.

Mr. KELLY. \$10,000. It is an aggregate of \$10,000.

Mr. DENTON. There is one place that it does not apply. The Reserve officer that went in between 40 and 45, I believe. That is one place it does not apply.

Dr. SHANNON. It also does not apply for Space; it does not apply for the Atomic Energy Commission in basic personnel legislation. There are exceptions in these agencies.

Mr. LESINSKI. Mr. Chairman, at that point, the basic intent of the law by the Civil Service Committee is to eliminate dual compensation for high-ranking retired generals would set up a private corporation; the Army paying this corporation for which it should be doing. The purpose of the dual compensation, we thought, was wrong. I have had since, some conversations with the civilian personnel that have been hurt, and I think the law should be amended. It should stay basically as this, but it should be amended to take care of the situation.

Dr. SHANNON. I am glad to hear this, Mr. Lesinski. We have suggested to the Department specific amending language insofar as it relates to professionals in the Public Health Service being excluded in much the same way as they are for the Veterans' Administration and the like.

We have lost some very good people who take advantage of the 20-year retirement, for example, within the armed services, who have been very anxious to come on our programs, but who have not been able to face this period of 5 years without coverage at this particular period in their life. As this provision has operated, at least on the professional side, we see actually a disadvantage to the Government.

Mr. LESINSKI. I know of one case back home where a fellow is making \$10,000. He is a retired military man and he has a promotion coming but he cannot take it because of this limitation.

Mr. DENTON. Do the widows have any rights now?

Under retirement of the commissioned services?

There was a time when they had no rights at all.

Dr. SHANNON. They have very little now.

Mr. LESINSKI. The intent of the law was—you have to agree—proper, but as in any law, there is always some ramification that you cannot foresee. This is one thing that should be amended.

Mr. DENTON. This is an old law. This was in effect when I was in the Army.

Mr. LESINSKI. Maybe before, but we just passed this particular law a couple of years ago.

NIH ABILITY TO DIAGNOSE AND TREAT DIFFICULT CASES

Mr. DENTON. Doctor, I probably spoke about this last year, but I want to congratulate you again on the way a case which came up in my district was handled by your agency, and I think this case ought to go on the record. Here was a young boy who was probably 5 or 6 years old—not older than that—who they thought, had a hopeless case of epilepsy. His father had taken him every place; he had been to every agency that could be thought of, and finally he was told there was no place to go but the National Institutes of Health.

He was taken to the National Institutes of Health, and within 10 days the NIH had discovered what was wrong with him. His father has to give him an injection every day, but he is perfectly normal and leads a perfectly normal life. I think you are to be congratulated on the way that was handled and I personally am always glad when I think of that case, that I have been on this committee, and have been able to help out in some small way.

This boy's father is very loud in your praise, all over my district. He said the trouble with you people is you do not tell what you are doing down there and he said, "I certainly want to let you know that I am going to tell what the National Health Institutes are doing in Washington," and again, I think you can be very proud of the work you did in that case.

I have had two other cases from my district where people have come to the NIH and have been helped greatly, and they are very loud in your praise and I think one trouble with this agency is the public just does not know what you are doing well enough. I do not think you advertise enough the work the NIH is doing. When you get these particular cases I think the public ought to know what fine work you are doing.

Dr. MASLAND. I would like to take that word back to the staff because it means a great deal to know that what we are doing is appreciated.

Mr. DENTON. I met this boy's father in a small town. He stopped me on the road. He said, "Well, the boy is getting along fine. If you are not going to tell what they are doing down there, I certainly am."

COLLABORATIVE STUDY

We were talking a good deal about this collaborative study. Would you tell me a little bit more about what is meant by that?

Dr. MASLAND. Yes. We are interested in determining the conditions which operate during pregnancy, and just at the time of birth, which may cause injury of the nervous system and lead to mental retardation or cerebral palsy.

One of the problems in the past has been that you never have accurate information, because these things take place at a time when you cannot observe their effect. The baby is injured while it is within the mother's womb, and nobody knows it is being injured. In our study, we are examining 50,000 women very carefully throughout the period of their pregnancy and making a record of all the things that happen. Then we examine the baby over a period of time to find out whether the baby is normal. If the baby is abnormal, we have a complete record for review to determine what has been responsible.

Mr. DENTON. How many studies are you making?

Dr. MASLAND. We have about 30,000 women so far, who have been studied. Our objective is to use this protocol for a total of about 50,000 mothers.

Mr. DENTON. How are these ladies selected for this case study?

Dr. MASLAND. They are selected on a carefully worked out statistical basis. In two instances, namely, the Boston Lying-In Hospital and the Philadelphia Lying-In Hospital, every woman who comes to the hospital is included in the study. In other institutions, a random selection is made so that the women selected for the study may be representative of the population of women who come to that hospital.

APPROPRIATION TRANSFERS TO OTHER PARTS OF PHS

Mr. DENTON. Now, there has been a rather large transfer from your agency to other parts of the Public Health Service.

Dr. MASLAND. Yes.

Mr. DENTON. \$4,242,000 for chronic disease and health of the aged and \$57,000 for communicable diseases.

Dr. MASLAND. Yes.

Mr. DENTON. Now, why was the transfer made from your agency to communicable diseases?

Mr. WIFE. This is something that Dr. Shannon mentioned this morning. It was part of a total NIH transfer to provide for centralization of community health research grants and related costs.

Mr. DENTON. What kind of work was it?

Dr. PRICE. I do not know specifically the content. What we have done is to take programs which were being financed out of this appropriation but which were being conducted by the Bureau of State Services and the Communicable Disease Center and have transferred the funds there.

In this case, I think this was probably grant activities that supported work in infectious disease related to—

Mr. DENTON. Childbirth?

Dr. PRICE. No. Related to neurological abnormalities.

Mr. DENTON. Now, you are no longer dealing with chronic diseases and health of the aged, I take it? that has gone to a new agency?

Dr. MASLAND. If you are referring to the service program of the Division of Chronic Diseases, Bureau of State Services, that is right.

SOURCE OF CARRYOVER BALANCE

Mr. DENTON. Now, I want to ask you about this item that is carried over, \$1,729,000. Does that mean that is money that is appropriated that was not used by your agency and which will revert to the Treasury if it is not used by the first of the fiscal year?

Dr. MASLAND. That is correct.

Mr. DENTON. From what did that \$1,729,000 come?

Dr. MASLAND. \$915,000 came from the research grant area; \$500,000 from training; and \$314,000 from the intramural program. Actually, in terms of our total budget, this is a rather small percentage. A very minor change in the approval rate of the applications which we have received would have eliminated this balance completely. There is a rather general impression among the public which worries me very much. There are those who feel that if a Federal bureau has money, they have to spend it. I believe we have documented here the fact that our crucial concern is the quality of the program. Although we may return to the Treasury as much as \$2 million this year, we have disapproved \$13 million worth of applications because they did not come up to the quality that we consider necessary.

Mr. DENTON. Were they turned down by the Advisory Council?

Dr. MASLAND. All along the line. Some of them were turned down by the study sections. Some of them were turned down by the Council and some of them were on the basis of staff decisions.

Mr. DENTON. But you have enough money to fund all of the applications you think should be approved?

Dr. MASLAND. That is correct. This year.

Mr. DENTON. I think that is all.

Mr. FOGARTY. Mr. Lesinski.

COLLABORATIVE STUDY PATIENTS MEDICAL EXPENSES

Mr. LESINSKI. How are these women paid who are included in the collaborative perinatal study?

Dr. MASLAND. They are not compensated for this. The observations which are made are a part of the routine procedure of pregnancy care and, in fact, these women are receiving a quality of medical care which is well beyond any compensation they could receive.

Mr. LESINSKI. In other words, instead of having an obstetrician to pay for, you handle their whole prenatal program, and after birth, taking care of the woman and child?

Dr. MASLAND. We do not pay the cost of medical care for them but what we do pay is the cost of observing their medical care.

Mr. LESINSKI. Are you paying the hospitals or the doctors?

Dr. MASLAND. We are paying, primarily, interviewers, who attain information about what has happened. We are paying people like the obstetrical coordinator, an obstetrician whose responsibility it is to review the records, and be sure the records are complete; interpret these records, and send us a report of the case. This is the type of payment which is being made for this study.

We are not paying for the cost of the patient's medical care.

Mr. LESINSKI. On page 17 you mention an enzyme called NA-K activated, ATPase. What is that?

Dr. MASLAND. In relation to the eye, is this?

Mr. LESINSKI. Yes.

Dr. MASLAND. This is an enzyme which has to do with the production of energy required for a number of different processes in growth and in living things. That simply refers to the name of the enzyme—to the chemical reaction which it facilitates.

ESTIMATED UNEXPENDED BALANCE

Mr. LESINSKI. I want to take this occasion to commend you, Dr. Masland, on your being one of the few that have come before us and had money to turn back at the end of the fiscal year 1963.

My apprehension about the whole Department—in fact, I heard this on a number of occasions—not recently but in former years, that there were funds left over and they were just expended for books or some other purpose, and that is contrary to the purpose and intent of the agency, and I commend you for your position.

I have no other questions, Mr. Chairman. Thank you.

Mr. FOGARTY. Is there anything else you would like to say?

Dr. MASLAND. No, sir.

Mr. FOGARTY. Thank you very much.

This is the last of the Institutes.

ABSORBING PAY ACT COSTS THROUGH PERSONNEL CUTS

Dr. Shannon, you were required to cut down personnel by 3 percent, I believe someone said. Who made that decision or recommendation?

Dr. SHANNON. This was a general decision made by the Secretary but it applies across the board except for certain exceptions that have been made for staff in medical care facilities of the Public Health Service. No exception has been made for NIH.

What we have had the ability to do is to move positions around to accommodate ourselves under the overall ceiling, so that it has not hurt the operation in a major way up to the present time.

Mr. FOGARTY. How could it affect next year?

Dr. SHANNON. Well, there are two things that would be affected in part by the reduction of personnel.

This will result in a reduction in our summer employment program. We will not have the positions with which to employ a large number of young, budding scientists who want to obtain within our laboratory an initial experience, an initial contact which may be important to their future interest.

It will not hurt most of our operations, and I think we may be able to make compensating adjustments in most cases, although, quite frankly, I am not certain: if we cannot make adjustments then we

will appeal for relief. We have two areas which are potential shortage areas. These would be in the new activities which have been established—namely, the Division of Research Facilities and Resources and the new National Institute of General Medical Sciences.

There is an increase in positions in the 1964 budget over 1963 in these areas. However, it is certain that every position in 1964 will have to be occupied, and even so, I think that the area of program development within those areas may be quite short.

So on balance, I would say, that for the most part the limitation has not seriously affected our operation up to the present time. As I have said, however, we may be deficient in the two new areas in the coming years; if we are, we will apply for an increase in position ceiling, then, we are still short, it would be because of the budget rather than the position limit because I feel quite sure the Secretary will relax this restriction if we can show good cause for the relaxation.

On the other hand, I think it may place a serious limitation on our summer program. I think this will be sharply curtailed.

Mr. FOGARTY. I was of the impression that you people thought this summer program was a good way of getting young people interested in this field.

Dr. SHANNON. Well, I think it is.

Mr. FOGARTY. It is a very essential program, isn't it?

Dr. SHANNON. Yes; but if the choice has to be made between the summer employee and the permanent employee, I think there is no doubt that the cut should be made in summer employment.

Mr. FOGARTY. I do not think there should be any problem in that regard. In the Department of Labor, they did not absorb any of these pay costs all the way down the line. I cannot understand why the Department of Labor would be more successful in holding their budget than the Department of Health, Education, and Welfare.

Dr. SHANNON. We have not been advised what next year's plans are.

Mr. KELLY. The 3-percent reduction applies to fiscal year 1963.

Mr. FOGARTY. How would that affect 1964?

Mr. KELLY. Well, the 1964 plans are reflected in this budget. They do not reinstate the positions that were abolished in 1963; but as presented to you, they are the positions for which the President is recommending funds in 1964.

Mr. FOGARTY. How will it affect the summer program?

Mr. KELLY. I am not aware of the problem that Dr. Shannon has discussed. We just completed a review of an analysis of the proposed summer employment for the Department, which can be financed and staffed within the authorized positions and, as I recall, for the Washington area it adds up to 763 summer employees for the Department and the largest number of these are at NIH.

Dr. SHANNON. I may be completely wrong but my personnel officer told me just last week that he did not see how he could have a summer program of the same proportions as previous years, in the face of the employment limitations, and I would be glad, Mr. Fogarty, to report to you the facts that bear out that statement.

Mr. FOGARTY. All right. Give us the facts on it and place them in the record.

(The requested statement follows:)

STATEMENT OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

In connection with furnishing information requested by the Civil Service Commission, the National Institutes of Health advised the Office of the Surgeon General in February that a preliminary analysis indicated that a substantially smaller number of students could be employed this summer than the number employed in the summer of 1962. A more detailed review of yearend employment requirements in all categories has been initiated to ascertain the feasibility of increasing the summer students employment potential. It does not appear, however, that the National Institutes of Health will be able to approximate the 1962 program of 635 students.

The policy restricting employment in the Department of Health, Education, and Welfare, prompted by a Presidential directive dated October 11, 1962, was established in the interest of limiting staff in view of a growing concern over the size of Federal employment and in the interest of instituting economies in order to offset the cost of the Civil Service Pay Act in line with legislative intent at the time this measure was enacted. This policy, which places a specific ceiling on yearend employment, provided for a 3-percent reduction in planned full-time employment, including both permanent positions and so-called full-time temporary positions. The summer employment program is included in this latter group. The influx of summer employees occurs in June at the conclusion of the academic year; whereas the yearend employment of permanent staff occurs as a gradual buildup over the course of about 9 months as newly authorized positions for the year are filled. Permanent positions form the hard core of employment required in the current and subsequent year to sustain authorized program. Consequently, limitations on yearend employment would, by natural circumstance, have the greater impact on anticipated employment of temporary staff, including the summer employment of students.

REPORT ON COLLABORATIVE PROJECT

Mr. FOGARTY. We will place in the record the comprehensive report on the collaborative project, that you prepared at the request of the committee.

(The report follows:)

REPORT ON A COLLABORATIVE PROJECT FOR THE STUDY OF CEREBRAL PALSY, MENTAL RETARDATION, AND OTHER NEUROLOGICAL AND SENSORY DISORDERS OF CHILDHOOD

SUMMARY

The collaborative project on cerebral palsy, mental retardation and other neurological and sensory disorders of infancy and childhood representing a joint endeavor of the National Institute of Neurological Diseases and Blindness and a group of medical centers came into being in 1957. It is the objective of this study to determine relationships between factors affecting women during pregnancy and the neurological and sensory disorders of their offspring.

This undertaking has been developed as a collaborative effort, the members of the several institutions involved participate not only in the fulfillment of the requirements of the protocol, but also in its planning and design. A central office represented by the perinatal research branch, NINDB, serves as staff and coordinating center, and provides central services including data processing for the study. As a result, there have been created within the collaborating institutions strong centers for perinatal research staffed with individuals increasingly knowledgeable regarding this type of investigation, and already exerting a significant influence on obstetrical and pediatric practice and on medical education in this environment.

The study has developed all instruments and methods necessary for its conduct thus far.

It has enrolled, as of October 31, 1962, 30,500 pregnant women and is expected to reach its initial goal of 50,000 pregnancies by January 1, 1965.

The wealth of data being collected has far exceeded that which had been considered conceivable. As a result, it has become evident that the analysis of these data should be undertaken immediately rather than delayed until the completion of data collection as had originally been planned. Concurrent data analysis can have several important advantages. It can permit the simplification of the protocol by elimination of those items of information which data analysis indicates have been adequately studied. It can point to the need for inclusion of additional items required for further clarification of unexplained findings. It is already providing a desirable stimulus and encouragement to the scientists participating in the study, who now begin to observe the fruits of almost 5 years of labor, and who are having for the first time the opportunity to explore their special interests in the solution of obstetrical, pediatric and neurological problems about which they may have been concerned for many years.

However, the decision to undertake at this time a massive data processing and analysis program has placed a heavy burden on the perinatal research branch and the central data processing unit of NIH.

The results of a rather extensive series of analyses covering widely different subject areas will be reviewed by the collaborators in mid-1963. These analyses are expected to lead to increased flexibility and diversification of the activities to be encompassed within the project. In order to exploit the leads opened up by these analyses, the present central protocol will be simplified, and the study will be extended by the development of studies focused on the solution of specific hypotheses (for example, rigidly controlled studies, clinical trials, investigation of high-risk population). In addition, more intensive investigation of difficult areas such as effects of nutrition, medication and of complex emotional factors may be undertaken.

This diversification of effort will be paralleled by greater flexibility of effort within the collaborating institutions. Whereas to date, the major emphasis has been on the "central core study" comprising those items of information being collected in identical fashion by all collaborators, the study now lends itself to greater development of ancillary studies which involve limited subgroups of the institutions within the project.

Many of the collaborating institutions have now developed to the stage of being, in fact, centers for the study of the causes of neurological and sensory disorders of infancy and childhood. Their support as independent clinical research centers, each developing a broad spectrum of activities of which some may be collaborative and others not, would represent an administrative step which would parallel the technical development of the project.

THE FIRST PHASE IN THE DEVELOPMENT OF THE NINDB COLLABORATIVE PERINATAL PROJECT

Shortly after the establishment of NINDB in fiscal year 1951, it became apparent to the Director, Dr. Pearce Bailey, that an increasing number of studies indicated that many neurological deficits seemed to be associated with perinatal, natal, and postnatal damage to the nervous system. The most common of these were mental retardation, cerebral palsy, deafness, blindness, and epilepsy. The development of methods for pursuing these lines of investigation, therefore, began early in NINDB planning and their importance was first stressed before the House Appropriations Subcommittee in 1952.¹

A year later it was pointed out at NINDB hearings that mental retardation could be produced in guinea pigs by asphyxiation during the prenatal period. In these experiments, female guinea pigs in turn were used and one of the litter mates was delivered by Caesarean section to provide a normal control. Others of the litter were asphyxiated by blocking the placental circulation for a stated period of time, and then delivering and resuscitating them. The asphyxiated guinea pigs developed an enduring mental retardation as measured by the usual maze intelligence tests.

The guinea pig experiments led to analogous work with rhesus monkeys because of their unique intelligence at birth which can be objectively measured and compared to that of humans in the performance of purposeful acts in early life. To achieve this, Cayo Santiago, an off-shore island of Puerto Rico having a free-ranging colony of rhesus monkeys was acquired and the NINDB Laboratory of Perinatal Physiology in San Juan in cooperation with the medical school

¹ Years refer to calendar years unless otherwise specified.

of the University of Puerto Rico was established. It was thought at the time that the Puerto Rican project might eventually be integrated with a larger multi-institutional collaborative attack on perinatal pathology using humans as study patients.

While the concept of organizing a multi-institutional collaborative project for studies in perinatal morbidity wherein NINDB would serve as a central laboratory and coordination center dates back to 1953, yet the NINDB was still not sufficiently organized or adequately financed to launch such a program until 2 years later. Meanwhile, the project received encouragement from an NINDB collaborative effort directed to retrolental fibroplasia hastened the eradication of that disease. Furthermore, new studies, especially those from the Johns Hopkins Hospital, continued to emphasize the high incidence of pregnancy wastage or perinatal mortality rate of approximately 78 out of 1,000 births as well as giving estimates of the extent of perinatal morbidity. About 15 out of every 1,000 births, it estimated, continued to live on for many years but with serious disabilities such as cerebral palsy, mental retardation, epilepsy, deafness, or blindness.

Additional impetus was given to the project by progress made in showing that kernicterus, a severe form of cerebral palsy coupled with mental retardation, usually resulted from a blood incompatibility between mother and fetus (Rh factor) and by the discovery that brain damage often resulted in infants born of mothers afflicted with German measles, giving a clue to the significance of virus infections during the prenatal period.

At this time there were many weaknesses attached to proposed studies on perinatal morbidity causing slow progress in this field of investigation. Less than a handful of obstetricians were occupied with perinatal research; there was no research liaison between the obstetricians and the pediatricians and the number of pediatric neurologists was shockingly small. Nearly all neurologists were occupied with adult neurology and it was indeed difficult to find any except in France who had ever studied the newborn.

There were many other difficulties. To begin with, a patient afflicted with mental retardation or cerebral palsy as the result of a perinatal injury was usually not diagnosed as such until 1 to 5 years after birth. By this time, it was more difficult than not to obtain a reliable obstetrical history; there was no uniformity in the country's medical schools for recording prenatal, natal, and postnatal histories thus making comparable studies unreliable. Moreover, in the past, all these studies were retroactive, that is, they began with the death and postmortem examination of the patient and then traced back to the perinatal period in search of causative factors. Usually, the investigators could collect very little data and, as a matter of fact, could study very few cases.

To attack the problem head on and to collect valid statistical data, it was then considered that multi-institutional and multidisciplinary collaborative project should be organized with NINDB serving as a central laboratory and coordinating center. It was estimated that at least 15 medical centers should participate in order to have a sufficient number of cases for reliable statistical comparisons, and that the initial study would take from 10 to 15 years. Each participating center would have a team consisting of obstetricians, pediatricians, neurologists, and neuropathologists and psychologists as well as basic scientists and statisticians. A prospective rather than a retrospective approach would be used and a uniform protocol for the use of all participating institutions would be devised for the enumeration of significant prenatal, natal, and postnatal factors.

It was envisaged under the plan that approximately 30,000 to 50,000 pregnant mothers and their offspring would be examined. It was believed that a project of this sort would revitalize the whole field of perinatal research, provide important epidemiological data, produce leads which might be attacked through ancillary research projects and improve methodologies and the practice of obstetrics and pediatrics and pediatric neurology and shorten the period for developing preventive measures against mental retardation, cerebral palsy and other aftermaths of perinatal injury. It was a gigantic task for, in addition to the organization of a complex project involving multidisciplinary and multi-institutional collaboration, it called for the training of more research obstetricians, pediatricians, and pediatric neurologists.

Every year since 1952 at congressional hearings the importance of an exploration of the perinatal period to penetrate the veil clouding the origins of mental retardation, cerebral palsy, and other neurological deficits of early life was emphasized at NINDB Appropriations Committee hearings. The NINDB Director

and two scientists employed by NINDB visited the more important of the country's medical centers to probe their interest as possible participants in a comprehensive longitudinal collaborative study involving the cooperation of at least 10 institutions and using NINDB as a central laboratory and as a focal axis of exchange and integration. The response was remarkably good in view of the complexity of the problem and the drain of manpower and facilities it would entail.

As the NINDB program grew, it became more financially competent to launch such an enterprise. In 1954, the preliminary plans for the organization of a collaborative perinatal project were first revealed to the Appropriations Subcommittees of the House and Senate and work was begun on the preparation of a special protocol for the collection of clinical and postmortem data.

In 1955, the movement received a new and vigorous stimulus from the searching questions and the emphasis of the need for more research in mental retardation by John E. Fogarty, chairman of the House Subcommittee. In May of the same year, the purpose and elements of the project were publicly announced in the Newsletter of Neurology and other media.

In December 1956, Yale and Brown Universities were the first of the several participating institutions to receive grant awards from NINDB under the expanding collaborative program. Yale's grant for the first year was \$107,799; Brown University received \$97,633. Previously, an ad hoc advisory committee composed of 15 scientists under the chairmanship of H. Houston Merritt had been convened to begin the preparation of a special protocol for the collection of clinical and postmortem data. During the same year, a 3-day conference was held in San Juan, P.R., to review the present status of research on perinatal influences which may lead to brain damage and impairment of learning, including a review of the work of the NINDB Perinatal Laboratory of Physiology in San Juan. The conferees consisted of leading investigators currently engaged in this type of research as well as members of the NINDB advisory committee for the collaborative perinatal project. It was sponsored jointly by NINDB, the National Science Foundation, and several voluntary health agencies: United Cerebral Palsy; Association for the Aid to Crippled Children; and the National Multiple Sclerosis Society. Also represented were the National Society for Retarded Children and the Muscular Dystrophy Associations of America.

Increased appropriations in 1957 permitted an acceleration of the program with respect to enlarging the number of collaborating institutions. Applications from five other medical centers had been reviewed and passed by NINDB special review panels and by the beginning of 1958, 12 institutions had joined the program so that there were then 14 collaborating institutions with a grant expenditure of \$1,389,527. Toward the end of 1958 two more were added, making the total support of the program approximately \$2 million. The participating institutions at that time were Boston Lying-in Hospital; Brown University; Charity Hospital, New Orleans; Children's Hospital, Philadelphia; Children's Hospital, San Francisco; Columbia University Medical Center; Johns Hopkins University Hospital; Medical College of Virginia, Richmond; New York Medical College; University of Minnesota; University of Oregon Medical School; Pennsylvania Hospital, Philadelphia; Yale University; The Children's Medical Center in Boston; University of Tennessee; and the University of Buffalo.

During the initial planning period, the NINDB advisory board had been expanded to include as cochairman, Dr. Nicholas J. Eastman, and added a statistical committee comprised of Drs. Jacob Yerushalmy, Carroll Palmer and Joseph Hodges. In addition, Dr. Stewart H. Clifford, assistant clinical professor of pediatrics at Harvard Medical School, and pediatrician-in-chief of the Boston Lying-in Hospital gave up his private practice to be coinvestigator and project director of the program at the Boston Lying-in Hospital and also to serve as consultant on a national scale to other groups collaborating in the program.

By midsummer 1957, it was obvious that the program was sufficiently complex to require the technical assistance of additional specialists in various disciplines to test and refine the protocol and to clarify the goals of the project. NINDB was most fortunate to recruit the services of Dr. Richard L. Masland, who came to Bethesda as Assistant NINDB Director but whose principal task at the time was to produce greater organizational harmony among the collaborators and to bring the project to the point where patients could be profitably studied and followed up.

During the fall of 1957, there was a detailed analysis of objectives and study design, work was carried forward on the development of methods of examination for the study, and the organizational structure of the central office and collaborating institutions was laid down. The pretest phase was launched in January 1958 and the first case actually registered in the study in January 1959.

OBJECTIVES AND DESIGN OF THE STUDY

The causes of certain disorders and conditions affecting children—cerebral palsy, epilepsy, mental retardation, defects of speech, hearing, and vision, organic behavioral syndromes, reading and learning deficiencies—are for the most part unknown. There is strong belief that the origins of these conditions lie in factors that come into prominence or in events that occur during the time period between conception and the early months of life, and moreover, that these factors or events are the precursors of congenital malformations and prematurity, or in the extreme case, fetal and neonatal death.

It is the purpose of the collaborative project to investigate the relationships among factors and conditions affecting parents and the occurrence and course of abnormalities in their offspring. The investigation is directed toward: (1) examination in depth of the effect of factors already suspect; (2) the identification of factors not presently suspect; (3) the elucidation of mechanisms by which factors operate.^{2,3}

Prenatal factors and conditions to be investigated include: (1) the conditions of pregnancy itself, such as infection, trauma, drug reactions, or the progress of labor. These include the normal and abnormal physiology of pregnancy, labor, and delivery; (2) the environmental factors—social and economic conditions, emotional stress, or medical care—influencing parents; (3) the biological factors—age, medical and reproductive history, immunologic characteristics—in parents, (4) the genetic background of the parents.

Other objectives of study research are: (1) the evaluation of the relation of prenatal factors to early and late fetal loss, prematurity, infant and early childhood mortality, and other aspects of the reproductive process and its outcome; (2) the dynamics of physical and mental development in early childhood, and the relationship of this development to genetic, biological, and environmental factors; (3) the evaluation of the significance of events in the postnatal environment in relation to the later development of disturbances of structure and function of the nervous system and other systems; (4) precise definition of the events of the reproductive process and the nature of its outcome.

In the pursuit of these objectives, a sample of 50,000 pregnancies is being studied, to insure the availability for long-term followup of at least 40,000 children. The children are to be studied until each reaches at least 7 years of age.

The study of the mother includes that of her past medical history and medical history since conception, her menstrual and gynecological history, her reproductive history, an infectious disease and systems review, detailed physical examinations and laboratory tests, interval histories during pregnancy, a detailed examination at the time of labor and delivery, detailed observations of the progress and complications of labor and delivery, and observations of anesthesia. Other measurements for study are the genetic and socioeconomic histories of the parents.

Evaluation of the child includes the observation of events in the immediate neonatal period, pediatric and neurological examinations in the newborn nursery, laboratory determinations during this period, 4-month pediatric examination with interval history, 8-month psychological examination with interval history, 12-month neurological examination with interval history, 18-month interval history, 24-month interval history, 3-year speech and hearing examination with interval history, 4-year psychological examination with interval history, and a final detailed examination at 7 years by members of such disciplines as neurology, pediatrics, psychology, speech pathology, and audiology.⁴

Study of pregnancy includes examination of the placenta, both by gross inspection and microscopically. Where pregnancy results in early or late fetal death, or when a liveborn child dies, pathological post mortem examination is made. In addition, the effect of virus infections during pregnancy on pregnancy outcome is investigated in great depth by serological techniques.

The essential element of this phase of the project is its prospective nature—the fact that information regarding pregnancy and labor must be obtained prior to any knowledge of the outcome thereof, and in anticipation of the probability that a certain percentage of the pregnancies thus examined will in fact lead to

² See app. A, original study objectives.

³ See app. 3, original study design.

⁴ See app. C, list of protocols developed and in use.

unfavorable outcome. Such a procedure, which experience has demonstrated to be essential if reliable data are to be obtained, requires the study of many normal pregnancies for the sake of having information on those which eventually prove to have been abnormal. In the case of rather frequent occurring abnormal outcomes, such as prematurity (10 percent), congenital malformations (7 percent), stillbirths and neonatal deaths (3.6 percent), and mental retardation (3 percent), the study of 50,000 pregnancies will provide enough defective offspring for many detailed analyses. In the case of less frequently occurring conditions, such as cerebral palsy (0.6 percent),⁵ however, the total number of case available for study (240) even in such a large project as this may be too small for some of the detailed analyses envisioned. In order to obviate this weakness, the study design has incorporated several mechanisms whereby additional numbers of "damaged" cases may be obtained for analysis. These involve the study of additional pregnancies using a greatly simplified protocol; the use of special protocol focused on a specific, limited objective, the special study of "high risk" cases as determined by the ongoing analysis of the study; the use of "stored data"—information or specimens (for example blood serum) which are obtained during pregnancy, but need to be subjected to extensive analysis only when the offspring proves defective; and the supplementation of the information obtained prospectively with other parallel information obtained by the retrospective review of hospital records of additional damaged cases. As the data analyses become available from the initial study of 50,000 pregnancies, this second phase of investigation is being developed. (For further information see "Future of the Collaborative Project.")

It should be pointed out, in the discussion of the objectives of the collaborative project, that the goal of the research lies in its application. It is the primary objective of the project to determine relationships among characteristics of women or the events of their pregnancies and the outcomes of these pregnancies; the ultimate and major objectives of the study is tacitly taken to be the development of public-health measures for the prevention of undesirable results of pregnancy.

As the project defines factors that assign patients to high-risk categories, it becomes necessary that physicians be able to identify those of their patients who should have special care and treatment. The development of the hospital record that will be adequate to screen the patient with a special risk, or the creation of methodologies in preventive medicine, are not functions of the collaborative project; it is the objective of the project, however, to provide the base on which these important public health programs can be undertaken successfully.

As of October 31, 1962, about 30,500 women were enrolled in the collaborative project; of these, about 24,000 had delivered and about 12,000 children had been examined at 1 year of age.

CURRENT STATUS

In many respects, the collaborative project is the largest undertaking of its kind in existence. Scientists in 15 leading medical centers across the United States, drawn from such diverse disciplines as obstetrics, pediatrics, neurology, neuropathology, virology, anesthesiology, audiology, ophthalmology, otolaryngology, speech pathology, pathology, chemistry, nursing, genetics, sociology, biometry, psychology, and epidemiology, have combined to investigate the broad problem of pregnancy wastage. In the course of this investigation, they are collecting and analyzing thousands of measurements—clinical, laboratory, and historical—for each pregnant woman and her offspring.⁶

In themselves, these measurements are of medical significance; they provide a panorama of the characteristics of pregnant women and the events of their pregnancies, and of the birth, growth, and development of their children, to an extent never before available to the medical investigator.

Pregnancy wastage, however, often stems from the complex interrelationship of many factors. The major value of the collaborative project derives from its ability to permit the association of study measurements, and to allow many avenues of approach to the understanding of a given neurological disease state.

⁵ See app. D, rate of different abnormal pregnancy outcomes actually observed in the study population.

⁶ See app. E, approximate number of completed study forms in files of Perinatal Research Branch.

It is precisely the paucity of strong hypotheses concerning the factors contributing to cerebral palsy, mental retardation, and other neurological and sensory disorders of infancy and childhood which led to a study design that was wide ranging and of massive scope.

Clearly, at this point in the course of the collaborative project, many of the interrelationships of greatest medical interest cannot be detailed. Not all of the cases for study have yet been enrolled; nor has any child been followed through 7 years of age. In fact only a few study children have reached 3 years of age. Because of the lack of knowledge regarding the significance of early neurological signs and symptoms and of early manifestations of delayed motor and mental development, very important medical conditions such as cerebral palsy and mental retardation will often not be identified until 6-7 years of age.

On the other hand, a sizable body of data, pertaining to a large number of cases, is available now. The scope of these data permit the evaluation of many facets of the problem under investigation. As a consequence, the collaborative project is currently engaged in the analysis of a broad range of detailed studies.

One class of detailed study with which the collaborative project is dealing is that of factors taken in association with the endpoints—fetal and neonatal death, prematurity, dysmaturity, congenital malformations—that are definable during the perinatal period. Another category of studies involves endpoints of an indirect and possibly transient nature, such as characteristics of newborn behavior, the immediate response of the newborn in the neonatal period, constellations of signs and symptoms suggesting the presence of neurological abnormality at the nursery examination or other examinations made during the first year of life.

Additional endpoints such as cerebral palsy, convulsive disorders, mental retardation, speech, language and hearing disorders will become available for study as significant numbers of children have undergone the later examinations.

Among the areas in which studies are underway is that of prior pregnancy experience, to determine the extent to which the outcome of a pregnancy can be predicted from the events and results of earlier pregnancies. For example, the collaborative project is measuring the probability that the birthweight of a study child, or its fetal or neonatal death, can be estimated from the outcome of the last prior pregnancy of its mother. It is making this measurement while taking into account the effect of basic characteristics of a biological and social nature—race, marital status, age and socioeconomic status of the mother, etc.

Among the strengths of the collaborative project is that it is a study of a number of cases sufficient to permit the simultaneous evaluation of many factors. Moreover, because there is a large number of participating institutions, the validity of findings can be tested by determining whether they hold across institutions.

Another area of current exploration relates the outcome of pregnancy to complications of pregnancy occurring during labor and delivery, or which affects the placenta. An example is an investigation into membrane complications—that is, the effects of premature or prolonged rupture of the membrane on incidence of stillbirths and neonatal deaths, in the presence (and absence) of certain maternal complications as toxemia, diabetes, or cardiac insufficiency; when the woman is treated with antibiotics; when she has or is free from intrauterine infection. The investigation inquires into these relationships with respect to factors such as the race, sex, birthweight, and gestational age of the child.

Many prenatal or perinatal conditions such as the presence of certain disease states in pregnant women or placental anomalies may have an important association with fetal and neonatal deaths; lesser manifestations of effect may be survival with a neurological deficit. For many of these conditions the collaborative project is able to study a larger series of cases than has ever been available. As an example a current study relates the number of umbilical arteries with fetal and neonatal death, and with congenital malformations. This is a complex investigation, with consideration being taken of the effects of such factors as birthweight and sex of the child, mother's age and her age at onset of menstruation, parity, type of delivery, placental weight, and resuscitation procedures applied to the child. The collaborative project is able to study a larger series of cases of a single umbilical artery than has ever been reported.

Collaborative project studies of differences in obstetrical techniques and methods of approach to various complications of labor and delivery are designed to measure the usefulness of these techniques and methods in preventing un-

desirable pregnancy outcome, and thereby provide indications for their use. A particular major obstetrical complication, which occurs in from 8 to 10 percent of pregnancies, is toxemia. The frequency of this condition permits the study of it in great depth.

Other particular studies now in progress are of the association of pregnancy outcome with specific characteristics of the mother—her height, weight, weight gain during pregnancy, early menstrual history, or the main course of her menstrual experience.

Many studies are based on the vast amount of laboratory data accumulated during the course of pregnancy, in order to test their use as reliable predictors of pregnancy wastage and as warning signal for special action to reduce or avert such wastage. Laboratory data under study include Coombs tests, tests for blood groupings, syphilis, hemoglobin, and hematocrit, and routine urinalyses for glucose and albumin.

The effects of environmental factors on health are a leading concern of researchers. This concern is reflected in the number of collaborative project studies devoted to the measurement of such factors as smoking, virus infections, and work history, in relation to the outcomes of pregnancy. Since the later health of the child may be affected not only by the course of his mother's pregnancy but by events occurring during the early stages of his life, the collaborative project is involved in studies of these events.

These detailed studies have a threefold purpose. Their objectives are to develop an understanding of the interrelationships of factors affecting the newborn child, to define predictors for estimating the probability of abnormality, and to guide the development of techniques for reducing abnormality. An example is the study of resuscitation procedures for reviving the newborn, undertaken to determine the effectiveness of these procedures in preventing death and promoting survival of healthy children, and as indicators of neonatal loss or neurological deficit in the survivor. Since there are marked differences in the applications techniques among the collaborating institutions, the measurement of effects of these differences on survival and child health are of considerable importance.

Other examples of studies of the newborn phase include the determination of effect of the level of bilirubin, a toxic chemical formed by the metabolism of the body, on the brain of the child, his survival and development. Bilirubin is assayed routinely in the newborn, and the meaning of levels is of general interest to the medical profession. Another test procedure of the newborn stage in which there is considerable medical interest is the Apgar score. The collaborative project is engaged in studying the value of Apgar scores, and the individual components of these scores, as indicators of neonatal distress, predictors of survival and of future mental and motor development.

It is anticipated that many of the studies discussed above will be reported at the scientific symposium⁷ of the perinatal collaborative project, scheduled for the late spring of 1963. Others, as they are completed, will be reported to the scientific community by the collaborating institutions at national meetings and through the mechanism of seminars held for local medical societies.

An indication of the emphasis within the collaborative project on study evaluation has been the formation of a studies coordinating committee, to minimize duplication of effort among the collaborating scientists in their analysis and interpretation of study data, and the creation of a publications review committee, to review their output before publication.

ACHIEVEMENTS

During the first years of the collaborative project, which were largely devoted to the collection of data, the collaborating institutions directed part of their effort to a program of associated or ancillary studies, undertaken mainly on a local basis. The aim of this program of ancillary studies was to take advantage of the initiative, experience and specialized interests of highly competent scientists participating in the study within the collaborating institutions. It was felt essential that each participant should be encouraged to develop special studies relating to the overall project, which however had not yet sufficiently matured for inclusion in the overall protocol or to conduct investigations of a limited nature capable of being encompassed within a single in-

⁷ See app. F, tentative agenda of scientific symposium.

stitution. The nature of the central study is such as to generate these ancillary activities and the two facets of the total study complement each other.

From the ancillary program, there have come numerous contributions in all fields associated with the main study, along with many identifications of areas, previously unrecognized, in which the central data will be useful for evaluation. The ancillary studies have been productive of facts, techniques, and methodology to an extent far beyond that anticipated for them.

In the field of virology the study has contributed much to the advance of serological investigations by the development and application of a microtechnique. This has been continually expanded and over 100 different viruses may be serologically evaluated in pregnancy. Almost all of these are currently being studied in complicated and normal cases. Also a significant contribution was made by this program to the work leading to confirmation of the identity of the German measles virus.

In the past, placental diseases and abnormalities have not been studied adequately or uniformly. Standard methods for examination of this organ have resulted from collaboration of numerous placentalogists. The collaborative project has stimulated an upsurge of interest in placental physiology and pathology. This has been reflected by studies devoted to defining the importance of this organ in pregnancy outcome. Ancillary studies of the placenta have identified poorly recognized or previously undescribed placental anomalies, diseases, and physiological aspects such as umbilical artery aplasia, amnion nodosum, vascular anastomosis in twin placentas, and methods of placental transfer.

The biometric assay of cervical dilatation, the establishment of various phases of labor, and the determination of abnormalities in the various labor phases have not only aided the understanding of the labor process, but have also provided the mechanism for accessing various labor patterns, in order that they may be adequately evaluated in respect to various pregnancy outcomes.

Ancillary endeavors have resulted in numerous biochemical studies concerned with maternal and neonatal physiology and pathology. These have resulted in a better understanding of the biochemistry of depressed or asphyxiated newborns, maternal hypofibrinogenemia and other coagulative disorders, enzymes in normal and abnormal conditions, mental retardation associated with amino aciduria, origin of amniotic fluid, and numerous other perinatal conditions.

Methods for evaluating the newborn and young child neurologically, physically, and psychologically have been generated by the requirements of the study. Movies demonstrating detailed neurological examinations of the newborn and 1-year-old child have been produced. These have received worldwide attention and are used as demonstration devices throughout the country. This accomplishment has had universal applications far beyond the confines of the collaborative institutions. Some of these have been electronic advancements in recording electrical activity of the brain and other organ systems, while others have been characterized by new and ingenious approaches such as utilizing detailed eye movements of newborn infants as a reflection of early signs of central nervous system damage associated with factors of pregnancy and delivery.

Appendix G⁸ lists, under 11 separate headings, some 400 publications of study participants, or by perinatal project-supported researchers, arising from this program. In addition, there have been more than 20 international presentations and exhibits developed on the basis of the ancillary research.

The course of the collaborative project has led to achievements that are peripheral to its main objectives. It has had an impact on patient care, particularly in the obstetrical and nursery phases, since the level of medical practice is improved when complete and meticulously systematic data are collected on each patient. The collaborative nature of the project has made an impact on medical schools by engendering interdepartmental research, and on medical teaching, by providing adequate case material and records. Since the study has become an integral part of the teaching and patient-care activities of the collaborating institutions, it has in effect influenced the training of medical students and young physicians at the intern and residency level. The importance of systematic documentation of medical information, the value of interdisciplinary and interinstitutional exchange of ideas and concepts, the opportunity of longitudinal studies to uncover the natural history of disease processes: these and other basic elements of this project are making an impact on the future physicians of this country.

⁸ See app. G, bibliography of ancillary studies.

It has stimulated research activities beyond that in which it is engaged, by helping to improve the research facilities of medical institutions, by improving the research staffs of these institutions, and by standardizing research methodology.

An important contribution of the collaborative project has been that it has reemphasized the importance in medical practice of the care of the well—the woman without complications of pregnancy or the well child.

Perhaps the most important of the incidental contributions of the collaborative project has been the interest it has fostered in collaborative research, not only in the United States but throughout the world. The study receives a constant stream of inquiries and visits from American and foreign scientists, who inquire into its protocols and methodology. Perinatal research has been stimulated in countries such as Uruguay, Great Britain, Denmark, and Sweden; collaborative study of the causes and effects of other disease states is an increasing phenomenon in American research.

MANAGEMENT OF COLLABORATIVE RESEARCH

THE DEVELOPMENT OF COLLABORATION

This study is unique in that its successful pursuit requires collaboration among a number of geographically and administrative separate institutions and, in addition, within each of these institutions, among scientists with widely differing skills and interests.⁹ In order to achieve this collaboration, a highly structured formal organizational pattern has been developed. It is built upon one essential concept—that within this study each of the professional participants has a responsibility not only for the conduct of the study, but also for its planning. The decisionmaking responsibility has rested increasingly upon the project director's committee—a group comprising an appointed representative of each of the collaborating institutions, and to whom are referred all decisions of procedure and policy. Professional and technical questions are referred to committees of experts representing the several basic disciplines involved in the study. The Perinatal Research Branch of NINDB coordinates the activities of these several committees and provides staff support for its functions. The proper and adequate conduct of the collaborative study is a complex and demanding undertaking. It is not surprising, therefore, that one institution was not prepared to carry the study beyond its pretest phase. Another institution has dropped out following the study of about 900 pregnancies and limited followup of the offspring.

PROTOCOL DEVELOPMENT

The study has required the creation of a series of examinations and interviews designed to elicit all important pertinent information regarding pregnancy and labor, and of detecting, at the earliest possible time, any neurological or sensory defects of the offspring. The original plan called for a final examination at the age of 5 years. Further study has indicated that in order to ascertain the important group of the mildly mentally retarded within this population, the final examination should be conducted following the first year of the child's school experience.

The creation, testing, and validation of the series of examinations required for this study has been until early 1962 the major task of the Perinatal Research Branch and the professional committees. There still remains to be developed the final test battery of the study, but the major portion of the task of protocol development for this phase of the study has been completed.

UNIFORMITY AND QUALITY CONTROL

An important asset of this study is the ability to compare the experiences of different segments of our population in widely scattered geographical areas. This can be accomplished, however, only if comparable data are received from each of the collaborating institutions. The use of a standard protocol is an essential element for achieving comparability. However, additional measures have been developed. These involve the use of special training sessions for personnel involved in data collection, exchange of personnel and exchange visits between institutions, and the maintenance of a central editing and data review

⁹ See app. H, the organization of the collaborative project.

procedure through which random or consistent deviations in data collection and reporting can be detected. In addition, the project directors have established a "performance committee" whose responsibility it is periodically to review the work of each collaborating institution to be insured of the quality of the data being provided.

FISCAL AND TECHNICAL REVIEW

The magnitude and complexity of this study have created a special problem of grants review. Because of the requirement for the participating institutions to adhere to a strict uniform protocol and in view of the existing differences in facilities, staff, interest, and the like, a careful review of the progress of this project in every institution coupled with the analysis of its fiscal needs is essential at frequent intervals. The adequacy of this review process is dependent upon thorough familiarity with the many administrative and scientific facets of this project as well as the specific problems and needs of every collaborating institution. As this project got underway the review of this study was the responsibility of an ad hoc committee on which several principal investigators served. This mechanism was not entirely satisfactory since it is desirable to separate clearly responsibility for the review of this study from responsibility for its conduct. Therefore, the review function for this project was assigned in 1959 to the Human Embryology and Development Study Section which has broad responsibility for the technical review of grant applications in the perinatal research area.

Because of many other responsibilities lack of time made it most difficult for this review board to give the project the kind of careful frequent attention which it deserves. For this reason there has been established in May of 1960 within the NINDB a Perinatal Research Committee (PRC) to assume responsibilities for the review of this project. This committee is composed of a panel of nongovernmental scientists in the area of obstetrics, pediatrics, neuropathology, pathology, sociology, epidemiology, biostatistics, and administration who have been selected because of outstanding scientific competence in fields represented within the study. This panel of experts advises the National Advisory Neurological Diseases and Blindness Council on the progress of the study and on research grant applications for support of the study. In addition this committee advises the Director, NINDB, upon his request on technical aspects of this study such as its conduct, and additional components proposed for inclusion in it. To fulfill its functions this group conducts an annual review of the fiscal requirements of each of the collaborating institutions, utilizing information provided by the Perinatal Research Branch regarding the institution's performance, a detailed breakdown of staff and expenditures, and project site visit where indicated.

Expenditures

PERINATAL RESEARCH BRANCH

Year	Positions	Amount
1955.....	11	\$50,000
1956.....	5	69,000
1957.....	14	148,000
1958.....	15	248,000
1959.....	42	715,000
1960.....	84	1,079,000
1961.....	114	1,154,000
1962.....	157	1,579,000
1963 estimate.....	187	1,957,000

GRANT FUNDS

1957.....	9	\$1,389,527
1958.....	8	1,101,506
1959.....	16	3,452,058
1960.....	16	4,631,665
1961.....	15	5,397,439
1962.....	15	5,906,276
1963 estimate.....	15	6,305,366

CERTAIN MANAGEMENT PROBLEMS FACING THE COLLABORATIVE PROJECT AT PRESENT
AND IN THE FUTURE

STREAMLINING THE DECISIONMAKING PROCESS

Based on experience so far, the present administrative structure needs to be carefully evaluated and revised with a view to streamlining decisionmaking, minimizing operational delays, maximizing flexibility in planning and design, and making optimum use of the project potential in moneys and talent.

It is obvious that to a large extent administrative delays are occasioned by differences in the potential interest and managerial problems within each of the collaborating institutions. Therefore, as leads emerge from the present phase of this study, it is possible to limit the exploration of certain leads to some institutions, of others to other institutions thus in fact creating smaller collaborating units. This development would constitute a major step toward streamlining decisionmaking and shortening administrative delays. Such a reduction in the size of the collaborating units would automatically enhance interpersonal, interdisciplinary, and interinstitutional communication.

In this connection, it is important that efforts be made to evaluate specifically the interest, facilities, available personnel, and available study population in every participating institution with an aim toward identifying those which might be specially capable of exploring certain major leads emanating from the present CORE study. Since interest and population characteristics are sufficiently different and numerous it is expected that every collaborating institution would be given an opportunity to make its further consideration in those areas in which it is most qualified.

It is further necessary to assure that data collected in this project are promptly evaluated and results distributed to all collaborators and to the scientific community at large. Leads emanating from the CORE study may require intensive basic research in certain aspects of pathology and physiology of pregnancy on a small scale before they could be further explored in a collaborative fashion. It goes without saying that basic research of this nature can best be done at the level of a selected few individual investigators.

PERSONNEL

The most serious single problem of the study has been the recruitment and retention of staff and personnel. The highly competent professional personnel required for this type of investigation are ordinary primarily trained toward imaginative and independent types of activity. The quality of imagination and strong personal motivation are needed within this study, especially in connection with its planning and direction. In addition, where the care and evaluation of patients is involved, a high level of professional competence is required. On the other hand, much of the work of the study is routine. The opportunity for personal achievement and recognition may be lost within the greater collaborative effort, and in such a long continuing study, the satisfaction of accomplishment may be delayed many years pending analysis of data. For these reasons it has been a serious problem to maintain the interest of top level scientists in continuing participation in the study. This problem exists both within the central office (the PRB, NINDB) and the collaborating institutions. Within the PRB, the problem has been aggravated by the fact that in addition to the above factors, salary levels commensurate with those available for individuals of equal competence elsewhere were not available. Some amelioration of this may be expected with the recent pay raise.

Within the collaborating institutions, the key effort has been to provide for each participant an opportunity to participate in the central planning of the study. The recent accelerated development of the data analysis phase is providing for the professionals within the program an opportunity to seek answers for specific questions relating to their own special areas of interest, and to participate in the study of the data and preparation of scientific reports.

There remains, however, one unresolved problem in this area. Ideally, the scientist participating in this study should be encouraged to have some independent activity of his own to develop related research ancillary to the main study, but exploratory in nature. Through this means new leads made apparent within the main study, may be further developed, and the genius of the scientist—his imagination and initiative—can be most suitably exploited. An effort has been made to define and support as separate independent ancillary projects,

many of these activities. Such piecemeal support, however, is not adequate for the recruitment of a stable staff needed for this study. It is difficult to define in advance many of these activities, which are usually exploratory or pilot in nature. Failure of the program to provide stable support for this type of independent activity can seriously limit the effectiveness of the total program. A number of the institutions have at this time developed to the stage where they are in effect centers for the study of the causes of the neurological and sensory disorders of infancy and childhood. The time has come for the independent development of these centers. The research center, or program project, provides the stable environment for the development of a broad and multidisciplinary effort. Within them can be encompassed many projects, all closely interrelated. The present central study will continue to serve as a clearly defined project, providing the essential background data and experience, and will further serve as an essential mechanism of collaboration and integration for a meaningful total program. At this stage the collaborative project has the potential to become a collaborative program.

PROBLEMS IN DATA PROCESSING

Although the project is well engaged in the analysis and medical interpretation of data, a large share of its present effort must necessarily be devoted to the steps preliminary to this phase.

Much of the early work of the project was in the development of protocols for data collection, and in the standardization of methods of collection in the various participating institutions. The instruments and methods currently in force reflect the experience and competence of many outstanding physicians and scientists.

A part of the effort of the collaborative study is still given to the review and revision of instruments for the collection of data. A much larger share goes into the continuing collection of study data, since only two-thirds of the number of cases to be studied have yet been enrolled.

The handling of the masses of data, including the review, editing, coding, and transcription, and finally, the machine processing, is a huge endeavor. These operations are the responsibility of the Perinatal Research Branch of the National Institute of Neurological Diseases and Blindness, to which the collaborating institutions forward their records.

By any standard measurement, the perinatal research project is a massive study, developing thousands of items of information on gravidæ and the results of their pregnancies.

As it was originally conceived, during the period of registration of the gravidæ and the growth of their children, the study would be devoted essentially to the collection and editing of raw data. Processing and evaluation of the data were taken to be problems that it was preferable to meet subsequent to, rather than concurrent with, data collection.

The staff of the National Institute of Neurological Diseases and Blindness made a comprehensive review of the progress of the study in the light of its objectives. It found that, while the goals for the data collection phase were being attained, several important problems had arisen which pointed the necessity for a considerable change in the operation of the Perinatal Research Branch.

The collaborative project is not rigidly controlled, with limited specifically defined objectives described in the most minute detail. It is, on the contrary, of such wide scope that its objectives are general, rather than detailed. New examinations are under development; old ones are revised, with consequent additions, deletions, and changes in study reporting forms; new problem areas of research relevant to the study, but for which interest has developed only during its course, are under consideration; related studies are proposed to shed light on particularly promising avenues of investigations. Even the appropriateness of the sample size of 50,000 cases is moot—is it too large, or too small, to meet the objectives of the study?

The best source on which to base the directions and conduct of the study are the data developed in its course. Data processing and evaluation must be started at an intermediate stage of the study, rather than only at its completion, if informed decisions are to be made as to its progress.

Moreover, the absence of a feedback of information so necessary to the proper conduct of the study had a concomitant, and no less significant, effect on the collaborating institutions. Physicians at the study institutions, while accepting as their primary responsibility the collection of data, never looked upon them-

selves merely as data collectors; it is a role in which they grew restive. They expected, with justification, that the efforts they exerted entitled them to participate in the development of the medical information contained in the data they provided, within a fairly reasonable period of time.

In order, therefore, to provide the project with the means for orderly direction and development, and to enable the institutions to collaborate effectively, the Perinatal Research Branch undertook a considerable addition to its workload. The Branch committed itself, and its collaborators accepted the commitment with interest and enthusiasm, to make available rapidly the study data, and to provide the collaborators with the services essential to proper evaluation of these data.

To fulfill this obligation, it was faced with a need to develop the means to process rapidly a huge amount of data into meaningful summarizations, and to manipulate the data as required for analysis.

In the past year, the Perinatal Research Branch, with the additional assistance of a large force of student summer workers, prepared, coded, and transcribed onto punched cards the complete backlog for many of the study forms. It developed, in addition, a machine technique by which it has been able to provide to the collaborators extensive sets of data for study.

The technique used to obtain the material for studies it has produced is makeshift, in the sense that in the interest of speed, elementary punched-card equipment has been used to do work that ordinarily would be done by electronic computer. Since the Branch has neither computer programs nor immediate access to the NIH computer facilities, many delays in processing information have been encountered. The central data processing facility has commitments to many other important programs and a correspondingly heavy work schedule. In addition, by moving up data processing by 2 or 3 years from the original plan, an immediate increase in the demand for central data processing services has resulted, for which the central NIH facility was unprepared.

There are other shortcomings in current methodology of the Perinatal Research Branch. It cannot produce the volume of data that is required with the equipment presently in use. Nor does it have the machine capacity to allow an intensive analysis of the data.

The greatest weakness lies in the inordinate amount of "turnaround" time required in the machine processing of data. While the sources on which PRB is dependent for machine work have given full cooperation, the new and heavy requirements have placed them under a severe strain.

As continued inroads are made in the backlog of raw data, and as collaborating scientists require more sophisticated analyses, demands for data processing will increase. It is apparent now that the major stumbling block is data processing capacity.

It is impossible to construct an adequate data processing facility on short notice. In fiscal year 1963, data processing expenditures are being doubled. A contract has been worked out with a private organization for card punching and other limited operations. The Central Data Processing Branch of NIH has created a night shift to meet some of the requests made by the Branch. In addition, it has assigned a group of computer programmers exclusively to PRB work to establish a data file to provide rapid access to the NIH computer.

The fiscal year 1963 effort, however, is merely preparatory to a full-scale operation which should come into being. This operation ideally should consist of a computer installation and an adequate programming staff within the Perinatal Research Branch, to supplement the central data processing facilities of the National Institutes of Health.

The establishment of a permanent data processing system for the collaborative project is anticipated for the latter part of fiscal year 1964. This system is expected to involve three separate machine installations.

The Central Data Processing Branch of the National Institutes of Health is expected to handle the bulk of the work for which a large computer is necessary. This arm of NIH, which in the past has provided the collaborative project with good support, is currently burdened with a heavy workload. The assumption that the Perinatal Research Branch will have ready access to the computer facilities of the Central Data Processing Branch is based on the expectation that the latter will shortly achieve the expansion that has been projected for it.

If the Central Data Processing Branch is able to commit a sufficient part of its resources to the collaborative project in fiscal year 1964, it is proposed that the project obtain services from this organization that will cost \$471,000. Proj-

ect expenditures for services from the Central Data Processing Branch for fiscal years 1965, 1966, and 1967 are expected to be of about the same size.

The project anticipates an expenditure in fiscal year 1964 of \$130,000 for contract services from a private data processing organization. This contract service is expected to provide the major share of card-punching and auxiliary machine services required by the project. Beyond fiscal year 1964, when the study will have less need of card-punching services, expenditures for contract work are expected to decrease.

The third component of the data processing system planned for the collaborative project is a small computer (the IBM 1401 system), to be part of a self-contained installation of the Perinatal Research Branch. It is anticipated that this installation, to be established within the Branch in the latter part of fiscal year 1964, will remove many of the delays occasioned by "turnaround" time. While the IBM 1401 system will be located physically within the Perinatal Research Branch, it is to be part of the Central Data Processing Branch of NIH, and under the ultimate control of that organization.

The data processing expenditures during the fiscal year 1964 within the Perinatal Research Branch itself, including the computer system to be installed in the third quarter are estimated at \$59,000. For fiscal years 1965, 1966, 1967 costs are expected to be about \$80,000 each year.

Thus, the total data processing need of the collaborative project during fiscal year 1964 is estimated at \$660,000. Projected costs of data processing for some years immediately beyond fiscal year 1964 are of the same magnitude.

FISCAL

Due to the expansion of program activities for fiscal year 1964, the personal needs of the Perinatal Research Branch are estimated to be at 239 positions. This increase is coming about in order to provide the necessary support for the increased data processing and analysis activities which the Branch is initiating. Some of the most vital data such as drugs taken during pregnancy can be processed only after extensive review and abstracting of physicians' notes, hospital records, patients' reports and other sources of information which the study is utilizing. In addition, with study children approaching 3-4 years of age, information relating to their language, speech and hearing development and function, and to their psychological performance, is collected creating additional staff needs. Thus \$1,872,000 are required in support of personnel and other objects (such as travel, supplies, equipment, rent, communications, etc.) in addition to the data processing and contracts noted separately below.

Data processing costs are estimated at \$660,000 as discussed before.

The effort to develop and produce the necessary viral antigens for the study of the effect of virus diseases in pregnancy on pregnancy outcome will continue in fiscal year 1964. The development of these reactive antigens has been supported by contract and has produced thus far 82 antigens.

An additional 42 antigens are in development and these include the antigens which have been found most difficult to perfect (Echo 24-28, Coxsackie A21-24, FEB, HGF, SV40, and the newer respiratory viruses). Continuation of the contract to develop these antigens is estimated to cost \$243,000. In order to develop satisfactory preparations of antisera from human volunteers to test the specificity of the antigens produced, continuation of the human volunteer studies at the Petersburg Reformatory is necessary. In addition, with the identification of the German measles virus, work is in progress to refine tests to detect German measles and to perfect a vaccine for German measles. The cost of the human volunteer work is estimated to be \$25,000.

In summary, it is estimated that the total budget needed in support of the direct operation for fiscal year 1964 is \$2,800,000.

Grants in support of this study in the collaborating institutions are estimated to require \$7 million.

FUTURE OF THE COLLABORATIVE PROJECT

The program of research into the problems associated with neurological deficiencies cannot be static. As wide as is the scope of the collaborative project, it still does not deal simultaneously with all areas with which neurological distress may be associated. There are basic reasons why this must be the case: to attempt to cover all areas of possible significance would place an insupportable burden on the structure of the collaborative organization. Certain areas, even

though suspect, have been excluded from investigation because the multi-institutional, collaborative approach does not apply. Moreover, the analysis and medical interpretation of data from this phase of the study will undoubtedly furnish leads to new fields for intensive investigation.

The key to the future of the collaborative project lies in the latter. In great part, the information derived from the continuing analysis of study data will determine both the future direction of the study and its form.

It is still too early to recommend specific changes in the study based on current evaluations, but it is appropriate to anticipate the general directions which they may take.

The analyses of data arising from the present protocol will make possible identification of factors associated with high-risk pregnancies. In some instances, there will be clear-cut definitions of factors that provoke undesirable consequences.

In other cases, the analyses of data will provide leads for further exploration, rather than the stipulation of well-defined relationships. In the main, it is toward these explorations that the collaborative project should devote its future effort.

There are several reasons why current analyses may provide leads, rather than complete definitions of relationships. In certain instances, for example, older women, say 40 and above, whose first pregnancies have resulted in breech presentations, the frequency with which a group presumably at high risk appears in the present study population is so small that it precludes the determination of definitive relationships. In these cases, the project will require a more extensive sampling of women with a given characteristic or set of characteristics than it is able to obtain under the present study design. Moreover, if the characteristic occurs mainly in a particular segment of the population, within some limited geographical area, the present protocol would have to be modified to permit an extensive sampling.

Where the mechanism of an action is difficult to determine, even though it is apparent that a group is at special risk, oversampling is not in itself a sufficient approach. In such cases, rather, it is necessary to go beyond the sampling design and scope of the present protocol for a study in depth. Older women, for example, are known to be greater risks during pregnancy than are younger women, although the reasons for this are unknown. It is therefore required to initiate specific studies of the physiology and pathology of pregnancy in older women, and of their endocrine system and metabolism.

The determination of definitive relationships, in some cases, requires a degree of control for which this phase of the collaborative project, and properly so, was not designed. To determine, for example, if a nutritional deficiency in pregnant women bears a relationship to pregnancy outcome, normally requires a closely controlled clinical trial. The collaborative project has the potential to develop such controlled studies based upon the levels developing from current analysis of the data.

An example of the use of such studies stems from the well-known fact that in the first 4 or 5 days of life there is a physiological drop in prothrombin levels. Since an excessive drop can lead to death through hemorrhagic shock, it is now a common practice to prescribe prophylactic doses of Menadione (vitamin K₃) or one of its water analogs for the newborn. Since it has developed that comparatively large doses of the vitamin can cause jaundice, the single prophylactic dose has been held at less than 1 mg.

In the last few years, it has become a practice to add Menadione to prenatal supplements, in dosages of 1 to 3 milligrams daily. This dosage exceeds several fold that considered to be safe for the newborn, and since it is taken daily for many months by pregnant women, the question arises as to whether the Menadione taken by the mother is a factor in the hyperbilirubinemia or jaundice of her offspring. The approach to the resolution of this question requires an adequately controlled clinical study.

A similar methodology is required for answering urgent questions about the effects on the fetus of certain drugs taken by women during the courses of their pregnancies. There are drugs, such as chloromycetin, certain sulfonamides, novobiocin, and salicylates, that are known to have a detrimental effect when administered in large doses to the newborn. The effects on the fetus of the drugs such as these, not infrequently given to pregnant women, are unknown.

The clinical trial is of value in other areas to which the future attention of the project might well be directed, mainly in the study of problems in the man-

agement of pregnancies with complications. Toxemia, for example, is a condition, readily identifiable in a woman, which, if it is not ameliorated, is likely to lead to eclampsia. The focus of the obstetrician is the pregnant woman; his immediate concern is to remove the threat to her. There may, however, be hazards to the child attendant on the management of the condition in the mother. The research into the comparison of therapies for toxemia, and into determining their effects on the fetus, is most likely to be productive in the environment of a carefully controlled clinical trial.

Again, the pregnancy complicated by diabetes is generally taken to be accompanied by a high risk of fetal or neonatal death. Urinary tract infections are believed to be associated with prematurity. As these judgments are confirmed by information developed in the course of this phase of the study, it will be appropriate to investigate, through controlled trials, whether these associations can be ameliorated by one or another type of management.

The evolution of the structure of the collaborative project largely depends on the extent to which it will have to undertake controlled clinical studies. The number of institutions participating in a given study will be a function of many things: the objectives of the study; the type of sample that is required; the equipment available or the medical practices in a particular institution; the methodology of the study—whether, for example, a sequential trial is feasible, whether it is supportable to administer a placebo, or whether a test method may be used without depriving a patient of therapy known to be effective.

Beyond future courses of study based on current evaluations of data, there are other areas to which the future effort of the collaborative project should be addressed. Perhaps the greatest strength of the project lies in the facility with which it can deal with the evaluations of medical techniques and procedures. Its present structure—many collaborating institutions, widely distributed—makes it ideally suited to the broad survey of the effectiveness of present-day methods and procedures dealing with labor and delivery and with the newborn period.

As illustrations, there have been reports in the medical literature suggesting that the use of outlet forceps has a beneficial effect on the fetus. Among the collaborating institutions, the use of outlet forceps varies from 5 percent of all deliveries to 40 percent. Because of the wide differences in the use of this method of delivery, it is evident that evaluations of the effects of this technique have not yet been sufficient to compel its universal acceptance. Nor have there been sufficient evaluations of the merits of elective Caesarean section or of the different types of management of breech presentation.

Similarly, there has been no definite study of the optimum level of bilirubin at which an exchange blood transfusion should be recommended. Since the procedure is not in itself without hazard, a delicate balance must be struck so that the advantages of an exchange outweigh the possible risks attendant upon it.

The collaborative project has many characteristics that lend themselves to the evaluation of methods and procedures currently in force. Beside the advantage of having many institutions to provide observations for comparison, there are the frequency with which procedures and methods are used, the detail in which factors important to evaluation are reported, the wide range of outcomes against which comparisons may be made, and the possibilities for measuring the reliability of conclusions, deriving from the consistency of results across institutions.

The understanding developing from this aspect of the collaborative research—the investigation into methods and procedures—provides the framework for future work in the evaluation of new techniques, as they are developed. One of the major weaknesses current in the field of medicine is the paucity of well designed, carefully controlled clinical trials of new techniques; it is rare that a trial of sufficient magnitude to permit definitive conclusions is undertaken.

In order to deal with the broad range of present methods and procedures, a large number of collaborating institutions is necessary. As specific new techniques are selected for test, these can then be tested in the institutions. Since the new techniques are supposed improvements over standard methods, no ethical considerations are involved, and the procedure under test can be compared with the standard, at the same institution, and with carefully selected, similar populations.

There are several major areas in which the collaborative project is currently developing information, but in which, because of the design and structure of the

project as it now stands, additional and other approaches are required for future investigations.

One of these areas is research into drug effects. The importance of the effect of medications on the embryo developing in utero recently has been re-emphasized by the catastrophe following the use of thalidomide in several European countries.

The collaborative project, from its inception, has made extensive efforts to obtain complete and detailed information about the administration of drugs to study patients. For certain drugs in common use—polio vaccines, influenza vaccines, etc.—it is in position to detect marked or subtle effects on pregnancy outcome. The fact that drugs of this nature are widely used, and are sufficiently well known so that women will recall having received them, simplify some of the problems connected with the study of their effects.

The project is also in a position to determine whether a drug that is lesser known and less frequently used has a deleterious effect on pregnancy outcome, provided that the effect were substantial and occurred in a large proportion of the children whose mothers used the medication. In such an instance, the retrospective approach will probably uncover the causative agent.

Although the present phase of this project can provide information on drugs with gross effects, and even on the more subtle effects of well-known drugs in wide use, there remains a considerable area of drug investigation with which the current protocol—and properly so—was not designed to deal. This is the area in which proper study requires the controlled clinical trial.

It has long been assumed that nutrition, and the effect of nutritional deficiencies in pregnant women, bears a relationship to the outcome of pregnancy. During the pretest phase of the collaborative project, attempts to assess the nutritional profile of pregnant women disclosed that there were many difficulties in determining their true nutritional state. Women enrolling in the study late in the course of their pregnancies simply could not supply adequate information about their nutritional status; even if they could, it is not possible to study the effects of 50,000 diets that are substantially different from one another.

A proper study of the effects of nutrition requires a degree of control for which this phase of the study was not designed. Such an investigation must be limited in the particular nutritional factors to be tested; for example, a projected study of the effects of diet on heart disease, by another scientific group, proposes to distribute patients into test and control groups, with completely specified diets for each group. A pilot study will determine whether such control is feasible.

Another approach to the measurement of nutritional factors in pregnancy outcome is to control not the individual, but instead, to test segments of populations whose nutritional quantity and variety is controlled by ecological and economic considerations. That this approach is feasible has been demonstrated by studies involving populations such as South American Indians, although there are many problems associated with such studies. Because of the complexities inherent in studies of nutritional factors, a careful review of available methods of assessments of nutritional adequacy with a panel of experts appears indicated at this time.

It has been pointed out that it is an objective of the study to identify the early clinical signs apparent in newborn or young children, that may be predictors of later motor, mental, and neurological development. The present lack of understanding of the meaning of many signs of abnormal newborn and infant behavior necessitates a prolonged followup of study children, causing problems of sample maintenance and imposing costs of money, time, and manpower.

As leads emerge from this investigation, therefore, it may be necessary to explore the value of newer methods of a more objective nature which are now being developed for the assessment of newborn function, to determine whether predictability can be enhanced by the utilization of these techniques. These newer methods deal with the assessment of neuromuscular function, newborn behavior, electroencephalographic activity of the newborn, the sensory threshold of the newborn, and the like.

As high risk factors operating in pregnancy are identified, and as sampling is stratified accordingly, a much higher yield of abnormal pregnancy outcome will be realized. The feasibility of such studies, then, as compared with the present, will be considerably greater, with the reduction in costs of professional time and other factors.

There has also evolved an increased interest over the years in the identification of minimal signs of brain damage in school-age children, and the study of the relationship of these to prenatal factors. Signs of minimal brain damage may be expressed in school performance and are due to disabilities such as reading and writing disorders. To assess these minute disabilities of major importance related to adequate school performance, followup studies of children would have to be continued beyond 7 years until they reach at least 10 years of age. Before such studies can be encouraged, the feasibility of a further followup should be evaluated carefully. Since the mobility of the study population varies in the different institutions and since the rate of loss to the study of patients differs considerably, institutions with a demonstrated high retention rate may be best equipped to handle the followup of children to ages greater than 7.

To a degree, the investigation of genetic factors within the framework of this prospective study offers problems similar to those pertaining to drug and nutrition investigations. For practical reasons, information about family conditions are obtained through the interview of the pregnant woman; these data are often, therefore, incomplete with respect to conditions existing in her husband's family, and indeed, in her own. Stronger genetics data can most likely be obtained by the additional interviewing of other members of the family (while drug information, once lost, is often irretrievable). With the identification of specific abnormal outcomes, retrospective studies, in which specific members of the family are interviewed for detailed information, become necessary.

The problems of emotional and maternal attitudes, and the manner in which they are related to pregnancy outcome, have not been identified sufficiently to permit intensive and formal investigation of them. Pilot work is necessary in this area to delineate the scope and direction of study.

Recent developments have suggested the importance of postnatal environmental sociocultural factors in relation to child development and behavior. In particular, the effect of environmental influences on mental performance may be of great importance. Unless the exploration of these factors is undertaken at some early stage in the life of the child, it may not be possible to differentiate the effects of biological prenatal factors and sociocultural postnatal factors on mental development and behavior. Again, pilot study is required to explore the means for measuring these effects.

The present detailed evaluations of virus infections as factors affecting pregnancy outcome explore systematically the effects of more than 100 different viral agents. Some viral infections occur relatively infrequently or are limited to certain geographical locations. As knowledge is gained in the course of the study, it may be necessary to adjust the sampling design so as to explore the effects of virus infections that are rare or occur in confined areas. If leads from the study suggest that the important effect of virus infection occurs early in pregnancy, a heavier sampling of women in the first trimesters of their pregnancies will be required.

To sum, the inquiry into the broad area of neurological deficits requires, by the very nature of the technical problems involved, a variety of approaches. The main approach, and necessarily the first, is the present prospective phase of this project. While this is a giant step in the total investigation, it is still merely a broad base.

The information developed from the present protocol will determine future undertakings, and the form that these researches will take. It may well be that, as the critical study areas are identified, the greatest benefits of research may come from investigations undertaken by limited groups of collaborators. Or it may be, with respect to major areas already identified as probably of medical significance, that different approaches, such as rigidly controlled experimental designs, with specific and limited hypotheses, should be formulated.

In this regard, with the present shortages of medical facilities and personnel, and with the considerable interest in research into the diseases of children that is current in other countries, it would be fruitful to coordinate efforts to take advantage of the original thinking and findings of other investigators.

APPENDIX A

OBJECTIVES OF THE COLLABORATIVE STUDIES IN CEREBRAL PALSY AND OTHER NEUROLOGICAL AND SENSORY DISORDERS OF INFANCY AND CHILDHOOD

The purpose of this study is to investigate the relationship between factors and conditions affecting parents and the occurrence and course of abnormalities in their offspring. This will be accomplished by analysis of pooled information collected in a uniform way in a number of medical centers throughout the country from women studied during pregnancy and from their offspring followed throughout infancy and early childhood.

The objectives of this study include a detailed investigation of the independent operative variables. It will be directed toward the reevaluation of the effect of factors already suspected, the elucidation of the mechanisms through which these factors are operative, and the discovery of factors neither presently known nor suspected.

The study will require accurate and detailed differentiation of the types of abnormality observed. For example a general classification of cerebral palsy would be inadequate unless by description or other means a consistent distinction is made among the numerous entities which might be grouped under this term. Such differentiation will require not only meticulous clinical examination but also equally precise pathological study whenever possible.

The factors and conditions which are to be investigated in the parents include:

(1) The conditions of pregnancy itself, such as infections, trauma, bleeding, drugs, and progress of labor. This includes, in effect, the normal and abnormal physiology of pregnancy, labor, and delivery.

(2) The environmental factors influencing the mother, such as social and economic conditions, emotional stress, and medical care.

(3) The biological factors in the parents such as age, parity, medical and reproductive history, and immunologic characteristics.

(4) The genetic background of the parents.

The abnormalities of the offspring to be evaluated are disorders of the nervous system of all products of conception at the time of delivery or appearing during infancy or early childhood, and including cerebral palsy, mental subnormality, behavioral disorders, and other specific neurological or sensory defects, as well as abnormality of other body systems.

In addition this investigation should make significant contributions in the following and other related areas:

(1) Evaluation of the importance of the above outlined factors in relation to the risk of early and late fetal loss, prematurity, infant and early childhood mortality, and other features of the reproductive process and its outcome.

(2) Dynamics of physical and mental development in early childhood and the relationship of this development to genetic, biological, and environmental factors.

(3) Evaluation of the significance of events in the postnatal environment in respect to the later development of disturbances of structure and function of the nervous system and of other systems.

(4) More precise definitions of the events of the reproductive process and the nature of its outcome.

The above outlined objectives, and anticipated method of procedure, imply a program of tremendous complexity involving the collaborative effort of a number of institutions and the coordinated activities of individuals of many disciplines. It involves a program which must be pursued in a uniform fashion over a number of years. Not the least of the anticipated benefits is greater knowledge of the method of conduct of such long-term, interdisciplinary, collaborative undertakings.

APPENDIX B

STUDY DESIGN FOR THE COLLABORATIVE STUDIES IN CEREBRAL PALSY AND OTHER NEUROLOGICAL AND SENSORY DISORDERS OF INFANCY AND CHILDHOOD

I. THE NATURE OF THE STUDY

This study is to be a collaborative prospective study, the object of which is to determine the relationship of certain biological, genetic, and environmental

factors in the parents to the occurrence of abnormalities of the products of conception.¹

The program involves the collaboration of a number of separate institutions throughout the country. For this reason it is essential that the study be conducted according to a single study design, and that the data be collected and recorded in a uniform fashion. The pooling of information in a central office, and its continuing analysis, is essential to the proper coordination of this program.

An essential feature of a prospective study is that the data recorded at any given time should not be biased by reference to events which have preceded, nor modified in the light of what develops subsequently. To this end, data must be recorded at the earliest possible time after the event reported upon and, for the purposes of this collaborative study, copies of the record of the event must be forwarded to the central office for coding, processing, and analysis without delay.

II. METHOD

In order to be able to define with accuracy the factors and conditions involved and their interrelationships, it is necessary that both mother and infant be subjected to detailed and meticulous examination. However, because of the low incidence of many of these conditions, and the multiplicity and interrelationship of the factors, it is essential that a large number of cases be studied. It is a serious question whether these two requirements can be met—that is, that detailed complete workups be obtained on a sufficiently large sample.

A solution to this problem lies in developing two complementary components of the investigation. One, whose emphasis is on detail and depth of study; the other so designed as to provide breadth.

One group of cases, carefully selected, studied, and followed, will be subjected to intensive investigation. This will provide detailed information, but on a relatively small number of cases.

The data obtained from these cases can be extended by the utilization of information already available from other patients in the collaborative institutions and in other institutions and agencies in the communities in which they are located. Such information is of necessity less detailed, but it can be obtained from a large number of pregnancies with a relatively small expenditure of energy.

The study thus comprises both an intensive and an extensive component as follows:

A. *The intensive component*

In this part of the study, it is necessary to obtain from the parents very detailed information regarding the genetic, biological, and environmental factors which might be operative, both before and during pregnancy. The pregnant woman is followed by repeated examinations throughout pregnancy and during the labor, delivery, and postpartum periods. It is also necessary to follow this with an equally detailed evaluation of the product of conception, whether from uncompleted pregnancy or at term. The evaluation of the offspring is to be continued throughout infancy and early childhood, and is to include general and special examinations at regular intervals, and pathological examinations whenever possible.

A detailed statement of the specific items of information to be collected and recorded, the times and types of examination, and the methods of collection of data will be developed by the collaborators and assembled into a detailed manual which will accompany the study design. It will be so designed as to include whatever information is considered pertinent to the purposes of this study. It may be visualized at present as encompassing the following listed phases:

- (1) Initial registration.
- (2) Initial interview.
- (3) Initial obstetrical examination.
- (4) General physical and neurological examination.
- (5) Prenatal return visits.
- (6) Laboratory examinations.
- (7) Labor and delivery.
- (8) The postpartum period.
- (9) Initial observations of the infant.
- (10) Subsequent periodic observations of the infant and child.
- (11) Special examinations, including pathological examinations.

¹ For details see the statement on objectives.

As stated above, for a study to be prospective, data relative to a certain circumstance or event should not be biased by reference to other circumstances or events which have preceded, nor modified in the light of what develops subsequently. To insure the attainment of this goal, the following specific measures are required:

(1) Data must be recorded as soon as possible after the event, and forwarded promptly to the central office for processing and analysis.

(2) Examinations should be conducted, and the results recorded, without reference to previous events or examinations. It is especially important that examinations of the infant be carried out without knowledge of possible favorable or unfavorable circumstances in the parents or in the environment. For example, in the case of a difficult labor, the evaluation of the neurological state of the infant may be biased if the examiner is aware of the circumstances of the delivery. Or similarly, an evaluation of the emotional attitudes of a parent may be biased if the examiner is aware of the fact that the child is showing evidences of instability.

It is recognized that the ideal is unattainable for the following reasons. In many instances the examination itself will elicit information relative to the previous events. In other instances the examiner himself may recall the pertinent details from a previous contact with the patient. In addition, the necessities of time and personnel may require screening or selection procedures which of themselves are an indication to subsequent examiners of the possible existence of an abnormality. Finally, medical care and ethical considerations often require that every possible means of evaluation be utilized.

Measures such as the following can, to some extent, serve as protections against the dangers inherent in these necessities:

(1) It should be the rule that at any examination the records of previous examinations should not be consulted until after the data of the current examinations have been recorded, and should they be changed as a result of consulting the previous records, this fact and the nature of the change must be recorded.

(2) An individual should be selected for special study or otherwise diverted from the mainstream only under the following conditions:

(a) Selection according to a plan approved by the advisory board.

(b) If selection is made on the basis of a screening test or other suspicion of abnormality, this fact must not be known to the second examiner until after he has recorded the results of his examination and the case must come to him among an unselected group including controls. In addition, subjects so selected must still be subjected to their regularly scheduled examinations in a routine fashion whenever possible.

The data which will thus be collected in the collaborating institutions will be pooled at the central office, processed, tested, and analyzed. The major effort in the analysis will be directed toward discovering associations between the recorded events in the child and the recorded events and circumstances in the parents. For example, the mothers will be subdivided into groups according to certain characteristics (environmental, biological, or genetic) which they or their husbands possess, and according to the course of pregnancy, labor, and delivery. The incidence of neurological and other conditions, and rates for pregnancy wastage and for childhood mortality will be studied in each of these groups.

B. The extensive component

As stated previously, the extensive component utilizes information available from other patients in the collaborative institutions and in other institutions and agencies in the communities in which they are located. It is assumed that nearly all frank cases of cerebral palsy and other neurological disorders are known to some public or private agency in the community, and that data relative to pregnancy, labor, and delivery are available with varying degrees of completeness. It is suggested that a specific plan be developed by the central office and the collaborating institutions to obtain and utilize the available data.

Briefly, the method would consist of two major operations:

(1) Attempts to identify, in the community, as nearly as possible all "damaged" children born in the area during the period of the study.

(2) Comparison of the course of their mothers' pregnancies, on the basis of data available in written records (mainly hospital records), with that of the other pregnancies which terminated in apparently normal children.

The "damaged" children who will be identified will come from among different groups of children, and the degree of completeness and accuracy of the obstetrical

information on them will vary accordingly. These groups may be listed as follows:

- (a) Those belonging to the intensive component.
- (b) Carefully followed offspring of "suspected" or "abnormal" pregnancies, or those showing "suspicious" signs during the initial hospital stay in the collaborating institutions, but not otherwise included in the intensive component.²
- (c) Those born in the collaborating institutions on the ward service, but not included in the intensive component.
- (d) Those born in the collaborating institutions on the private service, but not included in the intensive component.
- (e) Those born in other institutions in the community.

The detail, completeness, and accuracy of the data available will, of course, be greatest for group (a) and less in the other groups. It is the intention that the collaborating institutions, with the help of the central office, begin now to improve the records and the amount of detail in each of these groups. Specifically, it means that the data for group (c) be obtained insofar as possible with the same completeness and accuracy as for group (a); that the labor and delivery information for group (d) be kept with great care and accuracy; and that attempts should be made to bring as many as possible of the other hospitals in the area to adopt uniform prenatal, labor, and delivery records.

It is not expected that the collaborating institutions do all the record and other work on this phase on their own. The central office will carry the major burden of the statistical activities of this undertaking. The collaborating institutions, however, must be relied upon to insure that the data in their own institutions are kept in the desired detail, completeness, and accuracy, and to use their influence in the community to facilitate the obtaining of information on births in other hospitals and on the "damaged" children from the public and private agencies in the community. In some areas it may be possible to effect changes in the obstetrical records of some of the noncollaborating hospitals to make this part of the study even more significant.

It is not implied that all of the collaborating institutions will have the capacity for all of the above-mentioned portions of the extensive component. To the extent that each institution is able to contribute to the extensive component without significantly interfering with the intensive phase, the strength of the overall program will be enhanced. In addition, the National Institutes of Health will endeavor to assist in aiding other groups in the community qualified to contribute to the study, and to provide technical and statistical help wherever possible.

APPENDIX C

LIST OF PROTOCOLS—SYMBOLS AND CONTENT

(Prepared by collaborative study and presently in use)

Manual for obstetrical forms:

- AR-1—Obstetrical administrative record form.
- OB-2—Reproductive history form.
- OB-3—History since last menstrual period.
- OB-4—Gynecological history form.
- OB-4—Gynecological history manual.
- OB-5—Recent medical history form.
- OB-5—Recent medical history manual.
- OB-6—Past medical history form.
- OB-6—Past medical history manual.
- OB-7—Infectious disease and system review form.
- OB-7—Infectious disease and system review manual.
- OB-8—Repeat prenatal history form.
- OB-8—Repeat prenatal history manual.
- OB-9—Prenatal record form.

² Decision regarding the inclusion of this paragraph or a modification of it is still pending.

- OB-10—Return visit and laboratory record form.
- OB-11—Record of current pregnancy form.
- OB-12—Summary of hospitalization for any antepartum condition form.
- OB-30—Admitting record by obstetrician form.
- OB-30—Admitting record by obstetrician manual.
- OB-31—Admitting examination by obstetrician form.
- OB-31—Admitting examination by obstetrician manual.
- OB-32—Labor room record form.
- OB-32—Labor room record manual.
- OB-33—Delivery room events form.
- OB-33—Delivery room events manual.
- OB-34—Obstetrician's summary of labor and delivery form.
- OB-35—Anesthesia record form.

Recently revised OB forms are as follows :

- OB-40—Prenatal record.
- OB-42—Past Medical History.
- OB-43—Initial Prenatal Examination.
- OB-44—Prenatal Observations.
- OB-45—Laboratory Record.
- OB-46—Physician's Clinic Record.
- OB-47—Summary of Antepartum Hospitalization.
- OB-50—Admission History.
- OB-51—Admission Examination, Part I.
- OB-52—Admission Examination, Part II.
- OB-55—Delivery Report.
- OB-56—Obstetric Summary.
- OB-57—Anesthetic Agents.
- OB-58—Summary of Puerperium.
- OB-60—Obstetric Diagnostic Summary.
- PED-1—Delivery Room Observation of the Neonate Form.
- PED-1—Delivery Room Observation of the Neonate Manual.

COLR pregnancy questionnaire :

- FHH-1—Family Health History, Part I.
- FHH-3—Family Health History, Part III.
- GEN-5—Family History Interview—Outcome from Gravida's Prior Pregnancies.
- GEN-6—Family History Interview—Family Composition.
- GEN-7—Family History Interview—Health of Gravida and Her Family.
- GEN-8—Genetic Interview—Health of Baby's Father and His Family.
- CP-1—Notification of Patient Status.
- CP-2—Serum Packing Record.
- CP-5—Continuation Sheet for Obstetric and Pediatric Forms.
- CP-6—Editors and Coders Errata Sheet.
- CP-9—Report of Transmission of Specimen by Hospital—Neuropathologists Form.
- CP-9—Report of Transmission of Specimen by Hospital—Neuropathologists Manual.
- CP-11—Report of Blood Drawn.
- PED-2—Neonatal Examination Form.
- PED-2—Neonatal Examination Manual.
- PED-3—Nursery History Form.
- PED-3—Nursery History Manual.
- PED-4—Report of Fetal or Infant Death.
- PED-5—Results of Tests and Procedures Done on the Neonate Form.
- PED-5—Results of Tests and Procedures Done on the Neonate Manual.
- PED-6—Neonatal Neurological Examination Form.
- PED-6—Neonatal Neurological Examination Manual.
- PED-7—Summary of Hospital Course of the Neonate Form.
- PED-7—Summary of Hospital Course of the Neonate Addendum.
- PED-7—Summary of Hospital Course of the Neonate Manual.
- PED-10—Four-month Pediatric Examination Form.

PED-10—Four-month Pediatric Examination Manual.
 PED-11—One-year Neurological Examination Form.
 PED-11—One-year Neurological Examination Manual.
 PED-20—Followup Interval History Form.
 PED-20—Followup Interval History Manual.
 PED-29—Summary of Medical Records of Illness or Hospitalization Form.
 PED-29—Summary of Medical Records of Illness or Hospitalization Manual.
 PS-1-5—Manual of Directions for 8-month Psychological Examination.
 PS-1—COLR Research Form of Bayley Scales of Mental Development.
 PS-1—Manual for COLR Research Form of Bayley Scales of Mental Development.
 PS-2—COLR Research Form of Bayley Scales of Motor Development.
 PS-2—Manual for COLR Research Form of Bayley Scales of Motor Development.
 PS-3—Infant Behavior Profile.
 PS-3—Manual for Infant Behavior Profile.
 PS-4—Additional Observations.
 PS-4—Manual for Additional Observations.
 PS-5—Maternal Behavior in Testing Situation.
 PS-5—Manual for Maternal Behavior in Testing Situation.
 PS-10-17—Speech, Language, and Hearing Examination (Pretest).
 Autopsy Protocol.
 Outline of Neuropathological Proceedings.
 Procedure for Removal of the Brain at Autopsy.
 Examination of Placenta.
 PATH-1—Placental Examination—Gross Form.
 PATH-1—Placental Examination—Gross Manual.
 PATH-2—Placental Examination—Microscopic Form.
 PATH-2—Placental Examination—Microscopic Manual.

APPENDIX D

RATE OF DIFFERENT ABNORMAL PREGNANCY OUTCOMES ACTUALLY OBSERVED IN STUDY POPULATION—PRELIMINARY INFORMATION

	Rate per 100 births	Total births
	<i>Percent</i>	
Stillbirths.....	1.7	21,276
Neonatal deaths.....	2.0	21,276
	Rate per 100 live births	Total live births
	<i>Percent</i>	
Prematurity: 2,500 gms. and below.....	10.8	20,211
Gestational age: 36 weeks and below.....	15.9	17,808
	Rate per 100 children examined	Total number of children examined
	<i>Percent</i>	
Neurological abnormalities of newborn (observed).....	6.9	16,183
Neurological abnormalities of 4 months old (observed).....	1.2	8,613
Neurological abnormalities of 12 months old (observed).....	2.3	9,460
Psychological abnormalities of 8 months old (observed).....	3.4	11,489
Congenital malformations observed in 4 months old.....	6.2	6,192

APPENDIX E

Approximate number of study forms in branch files by form number and by hospital number as of Oct. 31, 1962 (from Perinatal Research Branch, COLR, NINDB)

Form No.	Hospital name and number												95, Yale	Total
	05, Boston Lying-In	10, Buffalo	15, Charles- ton	31, Colum- bia	37, Johns Hopkins	45, Virginia	50, Minne- sota	55, New York Medical	60, Oregon	66, Pennsyl- vania	71, Brown	82, Tennes- see		
AR-1-----	7, 246	683	1, 154	1, 917	2, 088	2, 147	1, 782	2, 364	1, 814	5, 303	1, 370	1, 720	913	30, 501
OB-2-----	6, 287	438	1, 157	1, 510	1, 544	1, 808	1, 649	2, 135	1, 792	4, 344	1, 103	1, 712	873	26, 352
OB-3-----	6, 303	412	1, 155	1, 474	1, 523	1, 756	1, 725	2, 353	1, 854	4, 476	1, 247	1, 681	854	26, 813
OB-4-----	6, 293	410	1, 161	1, 440	1, 483	1, 764	1, 652	2, 106	1, 750	4, 330	1, 210	1, 726	836	26, 179
OB-5-----	6, 281	411	1, 160	1, 495	1, 489	1, 749	1, 665	2, 347	1, 770	4, 269	1, 204	1, 721	842	26, 403
OB-6-----	6, 075	413	1, 184	1, 531	1, 573	1, 823	1, 652	2, 365	1, 773	4, 322	1, 208	1, 724	875	26, 518
OB-7-----	6, 274	415	1, 168	1, 419	1, 460	1, 775	1, 713	2, 353	1, 743	4, 334	1, 228	1, 718	875	26, 475
OB-8-----	35, 882	2, 596	7, 877	9, 911	10, 091	6, 550	11, 005	10, 096	7, 252	23, 736	5, 014	9, 175	6, 142	145, 327
OB-9-----	5, 286	279	1, 006	1, 446	1, 487	1, 858	1, 510	1, 722	1, 323	3, 987	794	1, 385	871	22, 954
OB-10-----	5, 191	270	963	1, 526	1, 468	1, 733	1, 486	1, 648	1, 320	3, 671	823	1, 347	857	22, 303
OB-11-----	5, 115	283	992	1, 507	1, 469	1, 682	1, 420	1, 682	1, 322	3, 267	788	1, 354	913	21, 794
OB-12-----	895	28	221	206	293	1, 175	293	139	1, 214	271	152	245	100	3, 049
OB-30-----	5, 723	245	1, 037	1, 751	1, 179	1, 692	1, 567	1, 604	1, 609	3, 886	917	1, 461	923	23, 644
OB-31-----	5, 662	260	1, 089	1, 750	1, 174	1, 704	1, 566	1, 557	1, 619	3, 884	919	1, 431	928	23, 543
OB-32-----	5, 513	273	1, 189	1, 666	1, 415	1, 747	1, 520	1, 524	1, 682	3, 913	878	1, 282	911	23, 513
OB-33-----	4, 958	265	1, 003	1, 398	1, 406	1, 671	1, 362	1, 513	1, 409	3, 696	821	1, 219	849	21, 570
OB-34-----	4, 991	227	872	1, 417	1, 043	1, 624	1, 335	1, 536	1, 410	3, 854	817	1, 237	854	21, 217
OB-35-----	5, 150	227	878	1, 371	1, 093	1, 595	1, 366	1, 500	1, 400	3, 678	813	1, 259	792	21, 122
OB-40-----	7				3		3							13
OB-41-----			8		39	8	3	2		33		118		3
OB-42-----	8				39	8	3	2						219
OB-43-----					47	7	3	2				3		63
OB-44-----	8		12	8	327	35	4	2		3		1		83
OB-45-----	31		133				4	2		3		7		542
OB-46-----						6	3	3						31
OB-47-----					26		3					6		56
OB-50-----	164	39	91	41	379	56	41					6		776
OB-51-----	164	39	91	41	379	56	41					6		776
OB-52-----	164	37	91	56	381	56	31					6		766
OB-53-----	153	38	83	38	356	58	37							725
OB-54-----	153	38	83	38	356	58	38							725
OB-55-----	152	39	81	38	347	58	38							715
OB-56-----	152	39	81	38	347	58	38							729
OB-57-----	171	38	98		353	393	37	13				10		1, 730
OB-58-----					352		37						120	1, 730
OB-60-----	514	17	2	16	2	16	17	54	320				23	2, 371
Pict 1-----	1, 028		14	165	344		210	176	236	172	58	26		2, 371
Path 1-----	4, 746	325	959	1, 382	1, 217	1, 204	1, 321	1, 572	1, 296	3, 306	1, 126	961	400	19, 815

Path 2-----	3,801	317	618	1,460	1,047	1,109	1,123	1,506	1,096	3,269	94	1,027	400	17,056
Path 3-----			9			3	13	20	9	55		2		134
Total OB forms-----	140,499	9,063	27,712	37,762	38,739	38,094	39,235	43,896	36,022	96,062	22,584	35,787	21,128	586,583
FHH-1-----	6,120	479	1,185	1,778	1,702	1,739	1,564	2,195	1,640	4,655	1,190	1,749	710	26,707
FHH-2-----	3,329	86	423	993	459	818	811	1,144	863	2,141	1,380	834	510	12,781
FHH-3-----	6,107	474	1,164	1,768	1,685	1,717	1,572	2,192	1,640	4,471	1,197	1,734	603	26,423
FHH-4-----	4,038	123	673	868	473	610	1,675	396	1,372	1,577	446	474	320	13,045
GHN-5-----	2,627	375	713	754	1,178	701	815	1,040	738	1,990	701	915	176	12,813
GHN-6-----	2,605	388	713	754	1,178	701	805	1,040	735	1,991	695	913	177	12,786
GHN-7-----	2,604	388	695	745	1,185	804	796	1,036	735	1,991	695	915	175	12,784
GHN-8-----	2,604	388	695	754	1,178	701	805	1,040	734	1,991	695	915	175	12,786
PED-1-----	6,470	235	1,014	1,617	1,592	1,786	1,495	1,699	1,601	3,852	1,203	1,533	784	12,765
PED-2-----	8,433	883	2,440	3,067	4,074	2,896	3,101	2,851	2,865	7,827	3,270	3,330	1,474	46,501
PED-3-----	5,335	313	1,072	1,497	1,752	1,837	1,501	1,723	1,527	4,238	1,206	1,509	1,786	24,296
PED-4-----	519	28	58	69	147	117	111	124	109	317	53	72	38	1,762
PED-5-----	3,885	298	972	945	1,130	1,125	1,053	1,249	1,064	2,031	1,109	1,275	499	17,235
PED-6-----	5,735	346	1,082	1,694	1,851	1,841	1,621	1,687	1,631	4,040	1,474	1,807	807	25,576
PED-7-----	5,239	293	988	1,478	1,520	1,703	1,425	1,688	1,494	4,091	1,118	1,440	754	23,231
PED-10-----	4,465	221	748	1,364	1,237	1,106	1,160	1,329	1,232	3,223	629	1,260	823	18,777
PED-11-----	3,202	64	460	1,152	1,049	780	978	837	739	1,980	466	1,043	555	13,314
PED-20-----	14,460	436	2,241	4,872	4,808	3,217	3,476	4,312	4,095	8,650	1,956	4,373	2,387	59,273
PED-29-----	976	43	89	874	439	207	169	308	724	615	229	174	246	5,093
8 Mo. Psych-----	3,839	160	582	1,055	1,130	896	880	1,048	832	2,348	547	1,119	552	15,008
Total FHH-GEN forms-----	30,034	2,701	6,261	8,414	9,038	8,061	8,843	10,084	8,456	20,807	5,999	8,449	2,936	130,083
Total PED forms-----	61,548	3,370	11,746	19,484	20,729	17,511	16,900	18,955	17,803	43,821	13,260	18,825	9,795	273,897
Total, all forms-----	232,081	15,134	45,719	65,660	68,506	63,666	65,038	72,935	62,281	160,690	41,843	63,061	33,859	990,473

APPENDIX F

TENTATIVE AGENDA FOR SCIENTIFIC SYMPOSIUM (JUNE 1963)

<i>Title and authors</i>	<i>Institution</i>
1. Cord complications related to survival and morbidity, Fisch and Spellacy.	University of Minnesota.
2. An obstetrical procedure (forceps) in relation to pregnancy outcome, Lyon, Spellacy, et al.	Do.
3. Investigation of specific aspects of prematurity, Westphal, et al.	University of Buffalo.
4. Relationships between methods of delivery of second-born twins and the status of second twins during the first year of life, Privitera.	Do.
5. Maternal status and its relation to pregnancy outcome, Lougrin.	Johns Hopkins University.
6. Cigarette smoking as a factor in pregnancy, Hardy, et al.	Do.
7. Prior pregnancy as a predictor of the results of the current pregnancy, Clark (to be given in collaboration with Dr. Elving Anderson, Minnesota).	Do.
8. The use of oxytocin and its relation to pregnancy outcome, Korones, et al.	University of Tennessee.
9. The height-weight relationships of the gravida, and its effect on the result of her pregnancy, Milan, et al.	Medical College of Virginia.
10. Differential development of twins, Holden, et al.	Brown University.
11. The type of delivery and its relation to the outcome of pregnancy, Benson, et al.	University of Oregon.
12. The weight of the placenta and its association with various characteristics of the placenta, Sedlis, Stone and Kim.	New York Medical College.
13. Anemia, and its effect on pregnancy outcome, Israel, Briscoe and Bishop.	Pennsylvania Hospital.
14. The age of the gravida and its relation to the results of her pregnancy, Israel, Briscoe and Bishop.	Do.
15. Serum bilirubin level in relation to the development of the child, Boggs, et al.	Do.
16. The duration of labor in association with the outcomes of pregnancy, Israel, Bishop and Briscoe.	Do.
17. Relationship of prenatal characteristics of pregnancy and dysmaturity, Clifford, et al.	Boston Lying-in Hospital.
18. Gestational age in relation to birthweight and the outcome of pregnancy, Clifford, et al.	Do.
19. Epidemiological approach to the study of birthweight, gestational age, and perinatal mortality, Sappenfield, et al.	Charity Hospital.
20. Toxemia and its effects on the results of pregnancy, Mule, et al.	Do.
21. The incidence of dysmaturity, and its association with prolonged gestation, primigravidity, and advanced maternal age, Stout, et al.	Do.
22. Clinical relationships of placental position in utero, Friedman and Little (PRB).	Columbia University.
23. Various aspects of placental pathology in relation to pregnancy outcome, Blanc.	Do.
24. The single umbilical artery as a factor in abnormal outcomes of pregnancy, Blanc, et al.	Do.

APPENDIX F—Continued

<i>Title and authors</i>	<i>Institution</i>
25. A study of the Apgar score in relation to various characteristics of the child, Kennedy, et al.	Children's Hospital of Philadelphia.
26. Brain weight and volume in relation to birth-weight and gestational age, Yakovlev and Lipkin.	Harvard and Perinatal Research Branch.
27. Lesions of the spinal cord observed at post-mortem examination, Yakovlev and Lipkin.	Do.
28. Characteristics of brains from stillbirths and neonatal deaths of diabetic mothers, Driscoll and Yakovlev.	Boston Lying-in and Harvard.

APPENDIX G

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APPENDIX H

ORGANIZATION

From the administrative point of view the project is to be conceived as a joint effort between two basic units, the Federal Government on the one hand, represented essentially by the Perinatal Research Branch (PRB) of NINDB, and an independent research unit, on the other hand, represented essentially by an element of a medical school and a hospital within a private or State university, designated as a "collaborative institution." All the other units involved in the project are mere amplifications both in staff and line dimensions, of these two basic units.

The director of the project at every medical school, called a project director, functions in three capacities:

At the local operational level in data collection, etc.

At the managerial or policy executive level, as a member of the project directors' committee.

At the policy formulation level as a member of the principal investigators' committee.

Whereas the Chief of PRB functions in four capacities:

At the operational level in coordination of data collection, in data analysis, specimen storage, etc.

At the managerial level, as a member of the project directors' committee.

At the policy level, as a member of the Principal Investigators' Committee.

As chief of his basic unit when functioning as a planning unit for the principal investigators' committee in design, data collection, data analysis, publication and evaluation.

The following summarizes the organizational framework of the perinatal research project showing the functions of each unit and its administrative relationships, in discharging such functions, with regard to its composition and line of authority-responsibility.

NINDB

The functions of this Institute in collaborative perinatal research may be described as follows:

The definition of the goal of Perinatal Research; the creation of a policy of collaboration in perinatal research; the delineation of the scope of collaborative perinatal research; the funding of all collaborative perinatal research thus delineated. In discharging these functions, the NINDB is advised by two bodies, the Council and the Perinatal Research Committee (PRC). The final responsibility of the collaborative research before Congress, the public and the academic world, rests with NINDB, as an arm of the U.S. Public Health Service. Finally, the delegation to Principal Investigators' Committee and to PRB of authority and responsibility of specific research decisions within the prescribed goal, policy, and scope.

COUNCIL

This is a group made up of citizens, professional and lay, selected by the Surgeon General from amongst a group of eminent scientists and civic leaders.

Functions

The Surgeon General of the Public Health Service empowers the Council with the authority to discharge the following functions for which they are held responsible to him:

To advise the Surgeon General on expenditure of Federal tax money on health (neurology) research in the United States and outside, and on related technical, administrative, fiscal, and political factors.

PERINATAL RESEARCH COMMITTEE (PRC)

This is a group of eminent professional experts in the various perinatal disciplines appointed by the Surgeon General of the Public Health Service.

Functions

The Director of NINDB empowers this committee with the authority to discharge its functions as outlined below for which they are responsible to him:

To advise NINDB on expenditure of Federal tax money in collaborative perinatal research in the United States and outside, and on policy, and scope

of such research; to review, for technical merit, all grant applications for collaborative perinatal research; to assist NINDB in evaluating progress of perinatal research.

PRINCIPAL INVESTIGATORS' COMMITTEE

These are senior professional persons (in obstetrics, pediatrics, pediatric-neurology) from all institutions involved in the project, whose names appear on each grant application and on whom rests finally the responsibility for the conduct of the study both locally, in their respective institutions, and in the project as a whole.

The Chief of PRB is a member of this Committee in his capacity as a Principal Investigator representing NINDB.

Functions

NINDB empowers this Committee with the authority to define more specifically the various policy decisions as outlined below for which they are responsible to it:

To define within established goal, policy, and scope of this research, more specific policy decisions regarding questions or hypotheses to be tested, design, methodologies, data collection, data analysis, data publication, research evaluation and administrative pattern of collaboration; to delegate to their representatives known as Project Directors, the managerial aspects of implementing these policy decisions; to delegate to PRB the professional aspects of planning in various steps of research.

PERINATAL RESEARCH BRANCH (PRB)

This is a branch of NINDB, with a Chief, two Assistant Chiefs (one medical and one statistical) and eight professional sections. Each section is likewise made up of medical (or psychology), and statistical, professional personnel, together with subprofessional and statistical clerks, secretaries and typists.

Functions

The NINDB empowers this Branch with the authority of discharging its functions as outlined below for which the Branch is responsible to it, administratively and to the Principal Investigators' Committee, professionally:

Produce protocol designs; prepare required procedure manuals; test various methodologies; establish pattern for inservice training shops; establish a pattern for the standardization of data collection; evaluate data collection; consultation with adequate subcommittees on professional problems in design and data collection; organize the Branch into sections with a Chief and Assistant Chief to each section and with roles assigned to perform within the respective disciplines the various functions outlined above. (Each Section Chief is directly responsible through the two Assistant Branch Chiefs to the Chief of PRB in both administrative and professional functions, but final PRB decisionmaking is made after due subcommittee consultation in the various sections has been performed; such decisions are forwarded to the project Director's committee for final decision and implementation through the Committee of Principal Investigators.) PRB is also responsible for data analysis and storage; specimen (pathology and virology) analysis and storage; coordination of data collection, of specimen collection and of publication.

PROFESSIONAL SUBCOMMITTEES

Each professional subcommittee is made up of a group of experts in any one of the project disciplines; e.g., obstetrics, pediatrics, psychology, pathology, speech and hearing, socioeconomic, sample maintenance, statistics, administration, interviewing, editing, etc., who are selected from a few collaborating institutions by PRB. They are called into executive session by PRB in the chair. Their term of office as subcommittees or as members is determined by PRB according to need.

Functions

These subcommittees are empowered by PRB with the authority to discharge their functions as described below for which they are responsible to it:

To advise PRB through its appropriate section on professional issues presented by PRB; to offer such advice only when requested by PRB.

PROJECT DIRECTORS' COMMITTEE

This is made up of professional persons (each one managing the study project in one institution) who are employed on a full-time basis. The Chief of PRB is also a member of this Committee. They meet in executive sessions once every 2 months, having a Chairman and Vice Chairman on a rotating basis. Decisions taken by them in executive session are arrived at by a voting mechanism, whereby each Project Director representing one institution has one vote; such a voting commits the respective institution to action and it is therefore expected that each Project Director consults with his Project personnel, especially the principal investigators, on all items of the proposed agenda before coming to such Committee meetings.

Functions

The NINDB through the Committee of Principal Investigators, empowers this Committee with the authority to perform the functions as outlined below for which they are held responsible to the Committee of Principal Investigators:

Meet in executive sessions several times a year to decide on administrative desirability and feasibility of various items in design, data collection, and data analysis as these effect every local institution and the project as a whole; represent and commit Collaborating Institutions in all decisions taken in executive sessions; create ad hoc or task forces (such as Performance Committee) as working bodies to perform various professional and administrative functions as need arises, with mechanism of reporting; creation of an executive committee (made up of its Chairman, Vice Chairman, and PRB Chief) to perform all functions in the interim between project Directors' group meetings; creation of inservice training shops; implementation of proper policy for publications; implementation of proper policy for evaluation; creation of various professional committees to act as advisers on professional issues referred to them by the Project Directors' Committee itself.

PROFESSIONAL ADVISORY COMMITTEES

These are made up of the senior professional representatives from every institution at the operational level in the disciplines of obstetrics, pediatrics, pathology, psychology, speech and hearing, sample maintenance, interviewing, and editing. The membership is for 1 year and each Committee elects its own chairman.

Functions

The Project Directors' Committee empowers these various professional committees with the authority to perform their functions as outlined below for which they are held responsible to it:

To advise the Project Directors' Committee on professional issues referred to it by the latter; to offer advice, only when requested by the Project Directors' Committee; to come into executive session by a call from the Chairman when issues are referred for advice.

THE COLLABORATING INSTITUTIONS

These are made up of the following:

New York Medical College	University of Buffalo
Johns Hopkins Hospital	University of Tennessee
Columbia University	Boston Lying-in Hospital
Providence Lying-in Hospital	Children's Medical Center,
Charity Hospital	Boston
Medical College of Virginia	University of Oregon
Pennsylvania Hospital	University of Minnesota
Children's Hospital of Philadelphia	Yale University

PRB is also considered, at the operational level, to be one of these collaborating institutions. These perform in the study under separate grants which are released by NINDB through the double review mechanism described before; PRB has a separate NIH intramural budget.

Functions (of each collaborating institution)

The Project Directors' Committee empowers each collaborating institution with the authority to discharge its functions as described below, for which it holds it responsible:

Data collection by various teams locally; submission of data-filled protocols and of various laboratory specimens in pathology and virology to PRB for storage, processing and analysis; case sample supply and maintenance; local inservice training; assistance to Perinatal Research Branch in design, analysis, publication, and inservice training; creation of local administrative pattern for discharge of above responsibilities:

(a) consultation with project board (dean of medical school, director of hospital and department heads involved) on administrative problems of a nonroutine nature locally;

(b) organization of the study into four teams, one for each of obstetrics, pediatric-neurology, psychology, and sample maintenance, with one coordinator or supervisor for each team, who is directly responsible to the project director via assistant project director;

(c) consultation with local principal investigators on professional matters locally;

(d) representation by the project director at Project Directors' Committee meetings to commit the institution with the vote taken;

And finally rendering available to perinatal study the following resources:

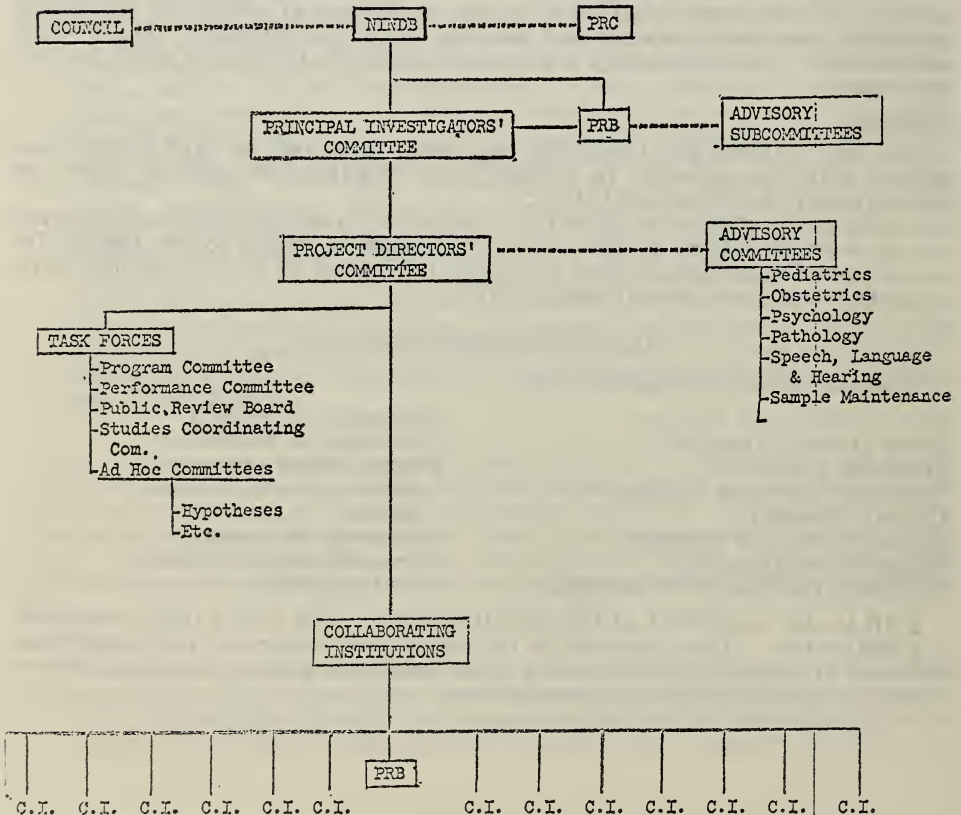
(a) patients according to an established sampling design and a sample maintenance procedure;

(b) service and teaching personnel (including availability of a centralized service to perform for the project adequate accounting of funds) as described by the project director;

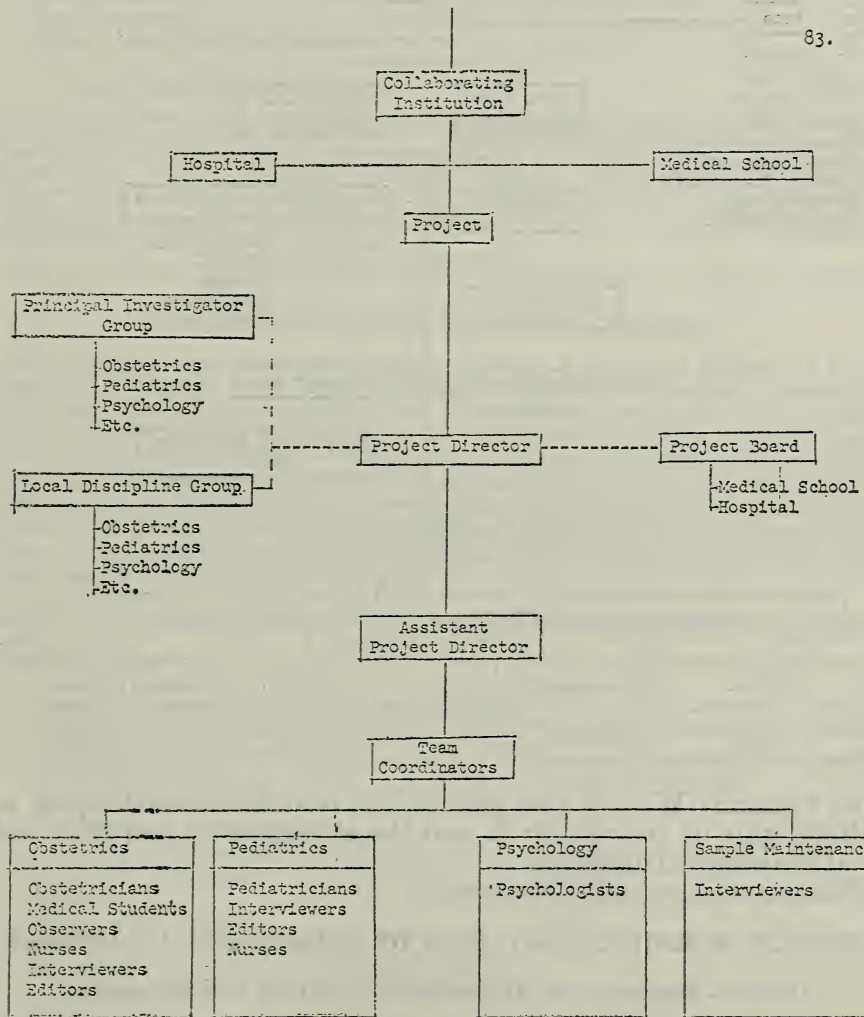
(c) premises, furniture, and equipment as outlined by the project director.

OVERALL ADMINISTRATIVE PATTERN OF COLLABORATIVE PERINATAL RESEARCH PROJECT

.82.

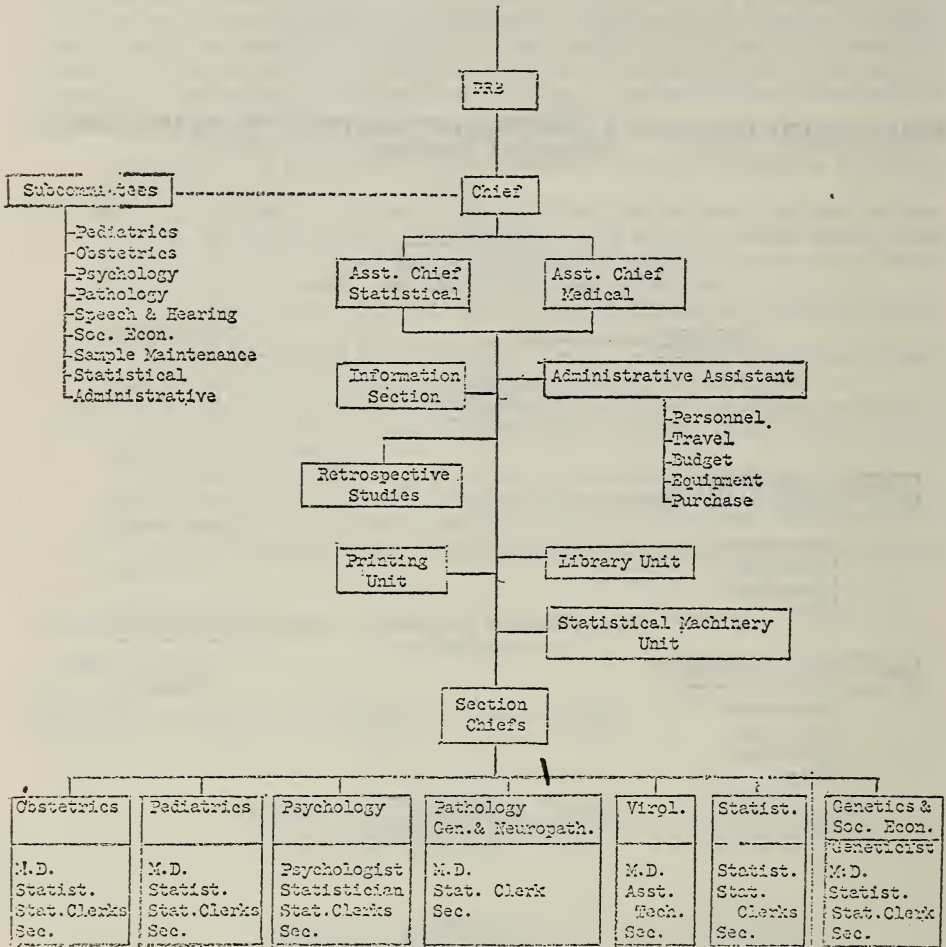


ADMINISTRATIVE PATTERN OF A COLLABORATING INSTITUTION IN THE COLLABORATIVE PERINATAL RESEARCH



ADMINISTRATIVE PATTERN OF PRB IN THE COLLABORATIVE PERINATAL RESEARCH PROJECT

84.



Mr. FOGARTY. We will also place in the record the usual report on the highlights of your research, and the statement on mortality and cost of neurological disorders.

(The material referred to follows:)

MORTALITY, MORBIDITY, AND COST OF NEUROLOGICAL DISORDERS

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases handled by the National Institute of Neurological Diseases and Blindness, and the estimated annual cost to the Nation.

I. DEATHS FROM NEUROLOGICAL AILMENTS DURING 1961 (U.S. NATIONAL VITAL STATISTICS DIVISION)

Category: ¹	Number
Cerebral palsy-----	1, 161
Cerebrovascular diseases (includes strokes and related brain ailments)-----	192, 951
Parkinson's disease (paralysis agitans)-----	2, 851
Multiple sclerosis-----	1, 432
Muscular dystrophy and related ailments-----	539
Epilepsy-----	1, 898
Myasthenia gravis-----	244
Amyotrophic lateral sclerosis-----	1, 068
Encephalitis-----	389
Brain tumors-----	4, 924
Spina bifida and meningocele-----	1, 195
Total, by reportable categories ¹ -----	208, 652

¹ The approximately 200 different neurological ailments pose unusual statistical problems. The cerebral palsy figure above includes categories 351 and 352 of the international classification of diseases but not the cases found in the undifferentiated "other" category number, 334. Mental retardation, blindness, deafness, and speech disorders are major neurological and sensory problems, but are not causes of death. Even in ailments for which deaths are reported, figures are unreliable because the chronically ill patient, weakened by disease, may die from an intercurrent infection and the death certificate may not record the basic neurological illness.

NOTE.—This is about 12.3 percent of the total U.S. deaths in 1961 of 1,701,522.

II. DISABILITIES FROM NEUROLOGICAL DISEASES

The National Health Survey Division of the U.S. National Center for Health Statistics estimates, from home interviews, that 220,000 persons consistently suffer some limitation in living because of headache or migraine. About 988,000 persons whose corrected vision is not sufficient to read newspaper are handicapped by this impairment in daily living. As the National Health Survey Division does not have figures on disabilities from specific neurological diseases, this Institute uses morbidity estimates from the respective voluntary associations. These statistics come from known experience with cases or from surveys of given areas. Some neurological patients, such as those with epilepsy, conceal their impairment to avoid job discrimination.

Total current number of disabled persons estimated

Disability category:	
Cerebral palsy-----	550,000.
Mental retardation (3 percent of the population; 126,000 born annually)-----	5,400,000.
Cerebrovascular diseases-----	Between 1,000,000 and 1,800,000.
Parkinson's disease-----	300,000 to 500,000.
Sclerosing disorders:	
Multiple sclerosis-----	250,000.
Other demyelinating diseases-----	250,000.
Muscular dystrophy-----	200,000.
Epilepsy-----	1,800,000.
Myasthenia gravis-----	30,000.
Amyotrophic lateral sclerosis-----	30,000.
Infectious neurological disorders (including encephalitis)-----	Over 1,000,000.
Brain tumors-----	Over 500,000.
Disorders of vision:	
Legally blind-----	392,500.
Partially seeing-----	2,019,700.
Disorders of hearing (totally deaf)-----	125,000.
With major hearing and speech defects, losing between 2,000,000 and 3,000,000 man-hours per day to industry-----	Over 3,000,000.
Disorders of speech interfering with normal development-----	2 to 5 percent of all children between the ages of 5 and 20.

III. ESTIMATED ANNUAL COST TO THE NATION

The estimate of neurologically disabled persons, excluding duplications for those with multiple disorders, is more than 10 million. Of these, approximately one-third are totally disabled. It has been estimated that the cost of care for the totally disabled and for a significant number of the partially disabled is more than \$5½ billion. Lost productivity to the Nation caused by these disorders may be more than \$20 billion.

During calendar year 1962, social security disability benefits of \$75 million were paid to 113,000 beneficiaries whose disabilities had begun in childhood. Of these disabled beneficiaries, more than 90 percent has neurological disabilities.

In fiscal year 1962, the Veterans' Administration sent \$424,475,064 in compensation checks to 410,404 veterans for service-connected disabilities, either psychiatric or neurological.

The annual cost to the States of the 195,000 mentally retarded persons in State institutions is estimated at \$250 million. No one knows the cost of supporting those in private institutions. Less than 4 percent of the 5 million mentally retarded are in institutions, public or private; the cost to individual families and communities for the other 96 percent is not known. It is estimated however, that the total cost of care of the mentally retarded is more than \$1 billion a year.

HIGHLIGHTS OF PROGRESS IN RESEARCH ON NEUROLOGICAL AND SENSORY DISORDERS 1962

(Items of interest on research studies conducted and supported by the National Institute of Neurological Diseases and Blindness.)

CHRONIC NEUROLOGICAL DISORDERS OF CHILDHOOD AND ADOLESCENCE

NINDB GRANTEES IDENTIFY BIOCHEMICAL DEFECT IN HEREDITARY BRAIN DISORDER

A study by NINDB grantees indicates that a rare hereditary disease of childhood, cerebromacular degeneration, may be associated with a metabolic renal defect. The disorder, which affects the eyes and brain of children at about the age of 6, results in blindness, mental retardation, and usually death. Through biochemical studies, the investigators have discovered that the disease is accompanied by an abnormal kidney function, which is also found in the parents, brothers, and sisters of the victims. This is manifested by the renal excretion of abnormal amounts of amino acids, histidine and 1-methyl-histidine, as well as carnosine and anserine.

In preliminary observations of three unrelated families, five members of which suffered from cerebromacular degeneration, the scientists found abnormal excretion which showed the body's inability to handle amino acids of the histidine group. The same abnormal kidney function also affected the victim's parents and some of his sibling's even though they had no symptoms of the brain disease.

The investigators suggest that the abnormal kidney function apparently is passed down from parents to children as a dominant trait, and the eye and brain defects are transmitted as a recessive trait. According to the authors, the fact that the two traits have been found in three unrelated families makes it likely that the renal and central nervous system abnormalities may be manifestations of the same gene.

Future studies of the biochemical abnormalities identified in these patients may result in the development of methods for correcting these defects. The finding that a similar genetic disease, phenylketonuria, can be treated by diet, suggests that prevention or treatment of cerebromacular degeneration may also be possible.

Drs. Samuel P. Bessman and Ruth Baldwin, pediatricians of the University of Maryland Medical School, performed this research and published their findings in *Science*.

NEW FINDINGS CONCERNING TREATMENT OF RH INCOMPATIBILITY IN NEWBORN MAY HELP TO PREVENT BRAIN DAMAGE

An NINDB study indicates that the albumin in the cord blood of infants with hemolytic disease due to Rh incompatibility has a lower binding capacity for dyes and for bilirubin than that of normal infants. In the infant with hemo-

lytic disease the binding capacity of the serum albumin for bilirubin is decreased; the bilirubin is thus free in and diffusible from plasma and can gain access to the brain. It is this free bilirubin that is generally believed to be toxic to the brain of newborn babies. In contrast, the serum albumin of normal babies is capable of binding the bilirubin and of preventing its entrance into and toxic effect on the brain.

To determine the dye-binding capacity of the cord serum, the investigators tested samples of cord blood from 45 normal infants and 27 infants with hemolytic disease. Binding of the dye phenosulfonphthalein (PSP) by serum albumin was measured, since this process is similar to the binding of bilirubin by albumin. Also studied were specimens of cord blood taken at the beginning and end of exchange transfusions from 37 infants with Rh and ABO incompatibility.

The present study, supported by a grant from NINDB, was made by Drs. William J. Waters and Eva G. Porter, Syracuse Memorial Hospital, Syracuse, N.Y., and was reported in *American Journal of Diseases of Children*.

NEW TEST MAY AID IN PREVENTION OF BRAIN DAMAGE FROM LEAD POISONING

A new diagnostic test for lead poisoning, which makes use of a drug used to treat the condition, has been developed by NINDB grantees. By measuring the amount of lead excreted before and after the administration of edathamil calcium disodium, investigators were able to detect even mild poisoning. The use of the test, especially in children, promises to facilitate early application of therapy to prevent residual brain damage.

The simple new technique proved effective in early or mild cases of lead poisoning not detectable by the usual test; i.e., determination of lead in the urine. Previously, laboratory confirmation of lead poisoning has been difficult, since there may be an overlapping of values for lead in normal and affected persons.

The study included 43 children: 8 with classic lead poisoning, 11 with suspected poisoning, and 24 who were presumed normal. The average excretion of lead 24 hours after administration of the drug was 165 micrograms of lead per liter of urine in the normal children, 995 in those suspected, and 1,966 in those with classic poisoning. As a result the grantees concluded that an excretion of more than 500 micrograms per liter indicated increased exposure to lead.

This study was made by Jo Anne Whitaker, M.D., William Austin, B.S., and John D. Nelson, M.D., of the Department of Pediatrics, University of Texas Southwestern Medical School, Children's Medical Center, and Parkland Hospital, Dallas, Tex., and was reported in *Pediatrics*.

CELL GROWTH AND MIGRATION TRACED IN POSTNATAL AND EMBRYONIC MOUSE BRAIN

This investigation of cell growth and migration in the brain of mice extends previous work to include studies not only with embryonic mice but also with young postnatal mice. The usefulness of autoradiography is demonstrated in tracing the development of tissue of the brain over a long as well as a short period of time.

To trace cell growth and development in the brain, tritiated thymidine (thymidine- H^3) was injected intravenously into pregnant mice at certain stages of the 19-day gestation period, and also into offspring of the mice at various postnatal stages.

Autoradiograms showed the following three patterns of development: (1) Most cells of the cerebellum from the 1st to the 15th day of gestation formed in the ependymal zone and migrated directly outward toward the external surface. (2) In the cerebellar ependyma, lateral caudal portion, the cells began to divide on the 13th day of gestation, then migrated over the external surface of the cerebellar anlage and continued to divide until about the third postnatal week. (3) From the 15th day of gestation onward the cells divided and dispersed freely throughout the cerebellum.

These studies led to the hypothesis that when two cell bodies and their sites of synapsis are within a circumscribed region of the central nervous system, the synaptic contact is established by cell migration during histogenesis. An example cited to support this hypothesis is the relationship between the Purkinje cells and roof neurons, which can be explained and predicted from known adult synaptic anatomy. Also, knowledge of the migration patterns should make possible predictions on synapses in other areas.

Dr. Irene L. Miale, now in Cairo, Egypt, and Dr. Richard L. Sidman, now at Harvard Medical School, performed this continuing study in the Laboratory of Neuroanatomical Sciences, NINDB, and they reported this part in *Experimental Neurology*.

EEG'S OF NEWBORN BABIES REVEAL BRAIN DAMAGE AND DEGREE OF MATURATION

NINDB grantees at the University of Oregon Medical School are demonstrating the values of routine electroencephalograms (EEG's), or brain-wave tracings, of newborn babies. With recent techniques for visual and auditory stimulation, using oscilloscopes, transistorized recorders, and lightweight ink writers, the sensitivity of the tracings has been improved. Normal babies as well as those born under abnormal conditions are studied, asleep and awake.

This work is a part of the current perinatal research program sponsored by the collaborative project on cerebral palsy, mental retardation, and other neurological and sensory disorders of infancy and childhood. Dr. Rudolf C. Engel, project director at Portland, Oreg., reported this continuing work in the *Journal-Lancet* (Minneapolis).

The brain-wave tracings made while the babies sleep differ considerably from those made during wakefulness. Also, the different stages from drowsiness to deep sleep can be distinguished on the tracings.

Visual stimulation by single flashes of light confirmed that the cortical response of the premature babies has a greater latency than normal. In post-mature babies, the latency is shorter. Highly significant, this difference in response time provides an additional scale for measuring the brain maturation at birth.

The response to auditory stimulation (by clacker) of premature and post-mature babies differed only slightly from normal.

Most striking of the abnormalities noted were the voltage depression which may be limited to one area of the brain or may be generalized, and the high-voltage focal spike and/or paroxysmal outbursts of epileptic discharge. The abnormal EEG's corresponded with the brain lesions found in these babies.

Dr. Engel presents various examples of normal and abnormal tracings, together with detailed information in each case, to demonstrate the value of electroencephalography in the neonatal periods.

LIMB MOVEMENT OF EMBRYO HELD ESSENTIAL TO NORMAL JOINT DEVELOPMENT

Congenital clubfoot (talipes)—one of man's commonest birth defects—may be caused by brief immobilization of joints before birth, according to a study of animals by NINDB investigators.

By administering curare (a paralyzing drug) to unhatched chicks, Drs. Daniel B. Drachman and Alfred J. Coulombre of the Laboratory of Neuroanatomical Sciences, NINDB, produced an experimental disorder similar to clubfoot as it occurs spontaneously in man. As more than one joint was usually involved, the experimental disease fulfills the definition of "arthrogryposis multiplex congenita."

In the chick embryo, intravenous infusions of curare for up to 48 hours caused transient paralysis which consistently resulted in limb deformities at the time of hatching. The limb disorders were clearly related to the chicks' embryonic position and the contour of the shell. The degree of deformity was increased by longer infusions, higher concentrations of curare, and older ages of the embryos. Chicks infused with control materials were normal.

Pathological examination of the deformed chicks showed that all normal structural elements of the limbs were present. In the affected limbs, joint rigidity was due to contracture of the skin, tendons, and ligaments, and occasionally to fibrous adhesions between the joint surfaces. No lesions were found in the spinal cords or skeletal muscles.

Although the cause of clubfoot has been unclear, clinical observations have previously implicated diseases or other factors which limit embryonic movement. By determining the exclusive effect of immobilization upon otherwise normal embryos, this study supports the hypothesis that prenatal limb movement is required for normal joint development. The study is reported in *Lancet*.

PARKINSONISM

IMBALANCE OF MOTOR NERVE SYSTEMS MAY CAUSE SYMPTOMS OF PARKINSONISM

The success of surgical therapy in Parkinson's disease may depend on destroying the loci of the brain which inhibit the indirect motor pathways (gamma route) and augment the direct motor system (alpha route), according to a study of cats by NINDB grantees.

The scientists suggest that the rigidity, tremor, and disturbed motor function in Parkinson's disease are caused by an imbalance of alpha-gamma activity, with gamma activity lowered and alpha activity increased.

The results of the studies showed that stimulation of specific areas of the brain heightened either alpha activity or gamma activity. Barbiturates abolished or reversed alpha activity, whereas ether facilitated alpha activity. In graded intravenous doses, chlorpromazine, a commonly used tranquilizer, also facilitated alpha activity, a finding which may explain why Parkinson-like symptoms are a possible side effect of this drug.

This study was made by Dr. Jack Stern, special research fellow of NIH, and Dr. Arthur A. Ward, Jr., at the University of Washington School of Medicine, Seattle, and reported in *Archives of Neurology*. (Dr. Stern is presently of the University of Texas Southwestern Medical School, Dallas.)

CEREBROVASCULAR DISORDERS

NERVES SURROUNDING CEREBRAL ARTERIES MAPPED BY NINDB GRANTEES

In an NINDB-supported study, scientists have traced the distribution of nerves around the cerebral arteries of man as well as animals. The investigators, by applying a well-known histochemical staining technique, have provided a simple and easily reproducible method of mapping macroscopically the distribution, extent, and structural characteristics of the periarterial nerves. Other organs and tissues of the body can also be studied by this method.

The histochemical technique employed was the Feulgen-Voit reaction, in which fuchsin-sulfurous acid (Schiff's reagent) liberates aldehyde from the nerves and stains them purple. The material used for this study was the cerebral arterial tree dissected from autopsy material of 46 humans, 6 monkeys, and 6 cats.

The investigators found that the periarterial nerves thus revealed are confined mainly to the tunica adventitia of the cerebral arteries. This finding agrees with recent data obtained by electron microscopy on animal tissue, including that of rats. Another finding was that the nerves around the cerebral arteries vary considerably in size, extent, and distribution. Also presented were preliminary data on the structural characteristics of these periarterial nerves.

Dr. Harry C. H. Fang, formerly of the Medical Center of the University of California at Los Angeles and now of the University of Alabama Medical Center at Birmingham, reported this study in *Archives of Neurology*.

EFFECTS OF CAROTID ARTERY COMPRESSION DURING ANGIOGRAPHY EXPLORED

Studies by an NINDB grantee indicate that routine compression of the common carotid artery during angiography, a diagnostic X-ray procedure, may cause a blood pressure rise within arteries, which is potentially dangerous in patients with recent intracranial hemorrhages. Fewer pressure changes were found, however when compression was applied higher in the neck—at the carotid bifurcation—and maintained for very short periods.

During angiography, compression of the contralateral common carotid artery is frequently performed to allow more accurate visualization of the vessels of the opposite brain hemisphere. In addition, the procedure is common to rule out the possibility of other lesions or to assess the secondary, or collateral, circulation.

The study was performed by Dr. R. Lewis Wright of the Massachusetts General Hospital, Boston, and reported in the *Journal of Neurosurgery*.

EPILEPSY

ORIGIN OF SEIZURE ACTIVITY IN IMMATURE BRAIN INVESTIGATED

One clue toward understanding the basic mechanism of seizure activity in newborns has been suggested by extensive studies of cerebral cortex in immature cats. Brain damage interrupting nerve fibers passing vertically from the cortex to

deeper brain centers causes horizontal proliferation and interconnection of nerve fibers, which is associated with increased excitability of the cortex.

Dr. Dominick P. Purpura, of Columbia University, has provided a general picture of the organization of nerve cells in the cerebral cortex of the immature cat and has described the manner in which this organization may contribute to the production of sudden, recurring electrical activity—similar to epileptic seizure activity—in the immature brain.

When lesions were made to isolate the cortex from subcortical regions the main descending axons degenerated. Further, axon branches of immature neurons proliferated laterally and made synaptic contact with adjacent neurons. Thus, groups of pyramidal neurons were linked in highly excitable closed circuits which were easily stimulated to seizure activity.

This summary report was made in *World Neurology*. Drs. E. M. Housepian, M. W. Carmichael, C. R. Noback, G. D. Pappas, and Mrs. K. Voeller of Columbia University collaborated with Dr. Purpura in many of the studies summarized in this report.

HEADACHE

HEADACHE STUDY SUGGESTS SOURCE OF MIGRAINE ATTACKS

In the preventive treatment of vascular headache, the action of UML-491 (1-methyl-d-lysergic acid butanolamide bimalate) on the blood vessels of the head appears to be significantly supplemented by its effects on the nervous system. NINDB grantees, in a study designed to define further the basic nature of migraine headaches, found that the reduction in responsiveness of the cranial nerves plays an important role in the prevention of this headache.

Various investigators have ascertained that the chemical is effective in reducing the number and frequency of vascular headaches in many patients if adequate levels are maintained in the blood, as by daily intake. An NINDB-supported study of the pharmacological action of UML-491 was undertaken in order to elucidate the pathophysiology of this sort of headache. These investigators determined that the chemical, besides its controlling action on vascular changes, has a sedative action in man which is an important aspect of preventive treatment of vascular headaches, such as migraine.

They consider that these observations support the idea that recurrent, increased sensitivity of the cranial blood vessels is an underlying cause of migraine headache.

The results of this study by Drs. D. J. Dalessio, W. A. Camp, H. Goodell, L. F. Chapman, T. Zileli, A. O. Ramos, F. Fortuin, R. Ehrlich, M. Cattell, and H. G. Wolff, of the Cornell University Medical College, Ithaca, N.Y., were reported at the VII International Congress of Neurology.

MULTIPLE SCLEROSIS

ROLE OF THYMUS IN DEMYELINATING DISEASES CLARIFIED

NINDB-NIAID grantees found that rats thymectomized at birth were resistant to EAE—an experimental disorder involving destruction of myelin which sheaths many nerves. By contrast, control animals developed the disease within 28 days after injection with tissue from an affected animal. The finding is another clue to the relationship between immunology and demyelinating disorders.

The thymus, functioning at its peak a few days after birth, produces lymphoid cells. These cells are liberated into the circulation and are deposited in the spleen and/or the lymph nodes. There they give rise to cells responsible for some—perhaps all—the immunological functions of the body. One of these functions, the ability of the body to produce antibodies, has been found to be inhibited by removal of the thymus soon after birth.

The present study suggests that removal of the thymus early in life also impairs another immunological function, the ability to develop delayed sensitivity to antigens. Thus thymectomized animals failed to acquire EAE, a disease believed to be mediated by delayed sensitivity. In addition they showed less delayed response to standard antigenic material (serum albumin injection) and slowed rejection of skin homographs.

The study, conducted by Drs. Barry G. Anderson, Branislav D. Jankovic, and Byron H. Waksman of the Department of Bacteriology and Immunology, Harvard Medical School, was reported in *Nature*.

PASSIVE TRANSFER OF EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS SUCCESSFUL
IN RABBITS

The first passive transfer of EAE (experimental allergic encephalomyelitis) and EAN (neuritis) with living lymph cells in rabbits has been reported by NINDB-NIAID grantees, Drs. K. Astrom, now of Sabbatsbergs Sjukhus, Stockholm and B. H. Waksman of Harvard University. Success in transferring the disease in rats has also been reported recently by Dr. P. Y. Paterson, and NINDB grantee at New York University Medical Center.

Of 21 rabbits injected intravenously with lymph cells from animals with EAE or EAN, 13 developed characteristic nervous systems lesions. Neurological abnormalities occurred 4 to 7 days after cell transfer, suggesting a delayed sensitization. Of 26 rabbits injected locally (intracisternally) 19 showed lesions and 18 showed neurological symptoms. In both cases, the intensity of the disease was related to the dose of cells, and control rabbits showed no symptoms or lesions. Only living, specifically sensitized cells produced either symptoms or lesions.

Although it is generally agreed that EAE represents some form of immunological reaction, passive transfer of the disease with serum from affected animals has proved impossible, and the role of humoral antibodies in the disease is unclear. The present studies seem to indicate that antibodies, specific for nerve tissue, are produced in response to challenge with sensitized lymph cells. These antibodies then attack the central nervous system, causing nerve sheath destruction and inflammation.

In addition, the study clarifies the actual mechanism of lesion formation, indicating that antibodies are cell-bound, rather than circulating freely in the blood, and that the circulating lymph cell mediates the delayed hypersensitive reaction. Furthermore, sensitized lymph cells injected locally were found to collect in the meninges and around veins penetrating the surface of the nervous system.

These experiments were conducted at Harvard Medical School, Massachusetts General Hospital, and the Karolinska Institutet, Stockholm. The study was reported in the *Journal of Pathology and Bacteriology*.

ROLL OF GLIAL CELLS IN MYELIN FORMATION STUDIED

A high level of metabolic activity has been found by NINDB grantees in certain glial (supporting) cells which are capable of "rebuilding" the fatty myelin sheath of nerve fibers after experimental damage. The glial cells were previously thought to be metabolically inert. The present findings, however, indicate a need for reappraising present concepts of the glial cells, especially their role in myelin formation.

The grantees produced, in cats, areas of myelin destruction—similar to that which accompanies multiple sclerosis—by repeated withdrawal and reinsertion of cerebrospinal fluid. Histochemical and autoradiographic analyses showed marked and significant metabolic reactions in glial cells in and around the areas of myelin destruction and regeneration.

After the myelin was destroyed, certain glial cells (oligodendrocytes) in the undamaged sheath were observed to enlarge, multiply, and show increased ribonucleic acid (RNA) activity. These modified cells then entered the lesions and formed the new myelin sheath. Most were converted ultimately into remyelinating cells (macroglia) or scarring cells (astrocytes). Autoradiograms demonstrated increases in the metabolism of RNA, NDA, and protein—an indication that, contrary to present beliefs, these cells are indeed metabolically active, responsive, and versatile elements of central nervous system tissue.

The study is reported in the *Archives of Neurology*, by Dr. Harold Koenig, from the Veterans' Administration Research Hospital and Northwestern University Medical School, Chicago; and Drs. Mary Bartlett Bunge, and Richard P. Bunge, formerly of the University of Wisconsin Departments of Anatomy and Zoology, now of Columbia University College of Physicians and Surgeons, New York. Dr. M. B. Bunge was a postdoctoral fellow of NINDB, and his work was supported in part by grants from NINDB.

NEUROMUSCULAR DISORDERS

NINDB GRANTEES CLARIFY RELATIONSHIPS BETWEEN MUSCLE AND NERVE ACTIVITY

Using microelectrodes to record from lobster and crayfish cells that respond to muscle stretch, NINDB grantees found that when muscles are stretched suddenly, the frequency of the resulting nerve impulses depends on the muscle's tension rather than its length. When stretch is applied slowly, both the tension and the length of the muscle influence nerve activity.

Studies of the little-known relationships between muscle activity and the initiation of nerve impulses showed that the stretch receptor cells of crustacea function according to certain basic principles. The scientists confirmed that, over a wide range of muscle stretch, the amplitude of the electrical changes which trigger the impulse (generator potentials) and the frequency of the impulses are both related linearly to the length of the muscle and logarithmically to the strength of the stimulus.

In addition, measurements showed that during muscle stretch, the nerve cell membrane became increasingly permeable to certain electrically charged particles, or ions. (Differences in the concentration and electrical charge of these ions are essential to nerve impulse transmission.) By comparing their results with other studies, the investigators concluded that the membrane permeability changes were not selective for a single ion—sodium—as previously thought, but that potassium and chloride ions might be included. These permeability changes are now being studied further.

This study was conducted by Drs. Carlo A. Terzuolo and Yoshiaki Washizu, Department of Physiology, University of Minnesota, and was reported in the *Journal of Neurophysiology*.

ACCIDENT AND INJURY

GLIAL CELLS SHOW INCREASED ENZYMATIC ACTIVITY IN BRAIN EDEMA

A histochemical study by NINDB scientists offers new evidence that glia (small cells interspersed among the nerve cells and fibers in the brain) display an increased enzymatic activity following brain injury associated with cerebral swelling. By demonstrating histochemically various oxidative enzymes (dehydrogenases), the investigators were able to show that astrocytes (one of the three types of glia) appeared to increase their enzymatic activity during the development of edema. Furthermore, this increased activity persisted long after edema had subsided.

This study was made by Dr. Lucien J. Rubinstein, visiting scientist, together with Drs. Igor Klatzo and Jaime Miquel, all of the Surgical Neurology Branch, NINDB, and is reported in the *Journal of Neuropathology*.

For these experiments, brain lesions in cats were produced by cold injury, with resulting swelling of the white matter of the brain. In the area of edema, certain enzymes displayed an increased activity in astrocytes within 12 hours, whereas other enzymes showed this phenomenon at later stages. The histochemical observations were correlated with other findings derived from application of specific staining methods for glia as well as by the use of fluorescein-labeled proteins in the same brain injury. Generally, the investigations indicated that the astrocytes are primarily implicated in the process of cerebral edema and emphasized the metabolically dynamic character of this involvement.

GENERAL DISORDERS OF THE NERVOUS SYSTEM

ORIGIN OF NERVE'S ELECTRICAL ACTIVITY CLARIFIED IN STUDIES OF SINGLE CELLS

Tissue culture studies of single nerve cells from mammalian brain suggest that neurons may not depend on connections (synapses) with other neurons for firing nerve impulses. By exact visual placement of microelectrodes, investigators have clarified the origin of spontaneous electrical activity in single cells, both nerve and glial, of kitten and rat brain.

Both the neuron body and the branched nerve ending, or dendrite, were found to be excitable and to fire "all-or-none" electrical impulses similar to those recorded from the nerve cells of intact animals. Contrary to previous findings, however, the spontaneous firing did not originate at the nerve synapse, since a neuron in tissue culture no longer has synaptic connections with other neurons.

In addition, the glial cells—the weblike, supporting structure of nerve tissue—were found to respond to strong electrical stimuli with a slow contraction. However, the current necessary to elicit the “glial response” was stronger than that normally produced by a nerve cell.

Dr. Walther Hild, head of the department of anatomy of the University of Texas Medical Branch, Galveston, collaborated in this NINDB-supported study with Dr. Ichiji Tasaki, formerly of NINDB's Laboratory of Neurophysiology, now with NIMH's Laboratory of Neurobiology. The work was reported in *Journal of Neurophysiology*.

NINDB SCIENTIST'S NEW TECHNIQUE OF PREPARING TISSUE FOR ELECTRON MICROSCOPE FACILITATES STUDY OF BRAIN

An NINDB scientist has developed a new technique for preparing tissue for electron microscopy whereby all parts of the brain can be immediately fixed and distortion is minimized. This method has greatly facilitated the study of central nervous system tissue, and is now widely used by other electron microscope laboratories. Dr. Sanford L. Palay, formerly chief of NINDB's Laboratory of Neuroanatomical Sciences and now professor of neuroanatomy at Harvard Medical School, perfected this technique and used it in an anatomical study of the cerebellar cortex of the rat.

Dr. Palay's method consists of perfusing the blood vessels with buffered osmium tetroxide, which hardens the tissue. It is then dehydrated, embedded in plastic, and cut in very thin slices for study.

Using this technique, Dr. Palay examined the glomerulus, a peculiar synaptic structure in the granular layer of the gray matter of the cerebellum. The electron micrograph revealed the glomerulus to be an “island” zone, without nuclei, and surrounded by clusters of neurons. Clearly seen in the center were the endings of nerve fibers (both axons and dendrites), which carry messages away from and to the cell bodies) and their synapses or junctions. Dr. Palay has described these nerve fibers in detail and also their adhesion to form the glomerulus. This anatomical description may provide clues that will lead to discovery of the specific function of the glomerulus, and an explanation of precisely how messages are transmitted from one neuron to another.

Dr. Palay's findings were presented at the annual meeting of the Anatomical Society of Great Britain and Ireland, in London, and published in the proceedings of that society.

NOREPINEPHRINE LOCALIZED PRECISELY IN SYMPATHETIC NERVE AXONS

As a result of the recent discovery of norepinephrine in sympathetic nerves, a unique technique has been used to pinpoint the exact location of the chemical which mediates nerve impulse transmission. By combining autoradiography with light and electron microscopy, NINDB scientists, cooperating with NIMH investigators, have demonstrated that radioactive norepinephrine and presumably endogenous norepinephrine are localized in those parts of the nerve axon containing small vesicles with dense central cores.

These findings were reported at the Fifth International Congress for Electron Microscopy by Drs. David E. Wolfe and Keith C. Richardson of the NINDB Laboratory of Neuroanatomical Sciences, cooperating with Drs. J. Axelrod and L. Potter of the NIMH Laboratory of Clinical Sciences. In previous biochemical and pharmacological studies, the NIMH scientists showed that labeled norepinephrine, when injected intravenously, is stored within sympathetic nerve axons or in certain cells (Schwann cells or chromaffin cells) closely associated with the nerves.

To define the location of norepinephrine more precisely, sections of pineal gland tissue from rats injected with labeled norepinephrine were coated with photographic emulsion. These were then developed and examined with light and electron microscopes. Blackened photographic silver grains resulting from the radioactivity were found to be localized over sympathetic axons lacking a sheath of Schwann cells (nucleated satellite cells). They were concentrated over only those portions of the axons containing numerous small vesicles with dense central granules.

The localization of norepinephrine is extremely significant, since these vesicles have been isolated and studied chemically, and their morphological characteristics can be determined with the electron microscope. In time, such studies will increase our knowledge of the functions of the sympathetic nervous system and

the action of drugs influencing the heart, blood vessels, and many other sympathetically innervated regions of the body.

DISORDERS OF VISION

DIGITALIS DRUGS MAY BE USEFUL IN GLAUCOMA THERAPY

A new treatment for glaucoma, an important cause of blindness, may result from preliminary experiments showing that the digitalis group of drugs is effective in treating certain types of glaucoma. Clinical trials by NINDB ophthalmologists indicate that digoxin, a compound obtained from digitalis which has been used for many years in treating cardiac failure, temporarily reduces intraocular pressure of patients with congenital glaucoma by inhibiting the action of an enzyme involved in the formation of eye fluid.

Drs. Kenneth A. Simon and Sjoerd L. Bonting, Ophthalmology Branch, NINDB, found that administration of digoxin to glaucoma patients suppressed the formation of aqueous humor by 45 percent, with a corresponding decrease in intraocular pressure. In the same patients, aqueous humor formation was decreased by 50 percent by the widely used drug acetazolamide and 65 percent by a combination of the two drugs.

These results suggest the possible usefulness of the drugs in the treatment of some forms of glaucoma. Their use could be considered where sensitivity or side effects preclude the use of other drugs such as acetazolamide. Unlike other glaucoma drugs, a single daily oral dose was found to be sufficient to maintain the patient's response in some instances. Combination therapy, although offering an increased effect, was not recommended because of the occurrence of side effects. The natural toxicity of these drugs, both acutely and through chronic accumulation, requires careful regulation of dosage.

The study was reported in the Archives of Ophthalmology.

These experiments were based on results of previous studies by these scientists showing that the enzyme—sodium-potassium activated adenosine triphosphatase—was abundant in such secretory tissue as the ciliary body of the eye, where aqueous humor is formed. When digitalis compounds were administered to cats, the investigators found that action of the enzyme was inhibited and aqueous flow was reduced. Clinical studies of glaucoma patients were then initiated with digoxin.

STUDY SHOWS ADRENALINLIKE AGENT INVOLVED IN LOWERING INTRAOCULAR PRESSURE

An adrenalinlike substance has been found to be involved in lowering of intraocular pressure. An NINDB grantee in Sweden, studying the effects of removal of the superior cervical ganglion, which temporarily decreases eye pressure, concluded that the decrease was due to the formation of adrenalin in the eye. Adrenalin (epinephrine) is used clinically to lower the eye pressure in patients with glaucoma.

Dr. Ernst Barany of Uppsala, Sweden, noted that 24 hours after excision of the superior cervical ganglion in rabbits there was a temporary increase in facility of outflow of aqueous humor from the anterior chamber of the eye, obstruction of which often causes the increased pressure associated with glaucoma. He conducted further experiments to determine by what mechanism the rate of outflow was increased. He found that the phenomenon, called the ganglionectomy effect, was due partly to the release of an adrenalinlike substance from the degenerating nerve endings in the eye.

This was concluded by the use of compounds which prevented the formation of epinephrine at the nerve terminals and others which blocked the effects of this compound at the site of action.

The conclusions reached were that after ganglionectomy an adrenalinlike agent is released from the iris or ciliary processes into the aqueous; the released agent acts on the trabecular meshwork, a spongy structure important for outflow. As a result the author concludes that an adrenalinlike mechanism may be operative in the normal regulation of eye pressure.

The work was reported in the Archives of Ophthalmology.

OCULAR HISTOPLASMOSIS PRODUCED IN PIGEONS

NINDB scientists have produced a progressive ocular form of histoplasmosis in otherwise immune pigeons by exposing them to a cold environment or by the application of steroids, coupled with injection into the eye of the responsible organism, *Histoplasma capsulatum*. In addition to clarifying the effects of temperature and steroids on histoplasma infection, the present experiments provide a valuable new resource for studying the role of histoplasmosis as a cause of human uveitis (inflammation of the eye's uveal tract, composed of the iris, ciliary body, and choroid).

Although *H. capsulatum* has been cultured from soil in and around chicken roosts, a progressive, active form of histoplasmosis had not previously been seen in birds. Drs. J. Lawton Smith and Dan B. Jones of Durham, N.C., initially injected the responsible organism into the eyes of pigeons at room temperature without producing histoplasmosis. Noting the exceptionally warm body temperature of the birds, they then placed a group of pigeons in a refrigerated room. Injection of the organism under these circumstances did produce the ocular disease. A third group of pigeons received injections of the organism plus injection of a steroid which lowers natural resistance. Again, the ocular disease appeared. Birds receiving both steroids and organisms likewise developed the disease.

By electrically recording both the body and eye temperature of the pigeons, the investigators noted that while basic body temperature of the refrigerated birds remained around 107.5° F, that inside the eye showed a marked drop. It is known that the fungus will not survive in temperatures as high as 107.5° F. These results appeared in Archives of Ophthalmology.

NEW COMBINED THERAPY FOR HERPETIC KERATITIS

Although steroids effectively reduce eye inflammation, they interfere with the body's defenses and may be dangerous in treating such infections as herpes simplex keratitis. Therefore, the combination of IDU (5-iodo-2-deoxyuridine) and steroids represents an important safeguard against the possibility that an inflammatory eye condition is of viral or infectious origin.

These findings followed previous studies in which Dr. Herbert Kaufman used IDU, a drug developed for use against cancer, to cure herpes simplex keratitis. This drug is the first to be proven effective against a virus disease of this type. However, IDU was not effective against certain other eye conditions, which are now treated with steroids.

Working with rabbits, Dr. Kaufman and his associate, Emily D. Maloney of the University of Florida College of Medicine, Gainesville, found that steroids alone made herpes simplex keratitis worse, as expected. However, when IDU was added, the keratitis was cured, in spite of the steroids. They concluded that the addition of IDU lessened the ill effects of steroids on herpes simplex keratitis.

Preliminary patient studies confirm the advantages of combined steroid and IDU therapy to treat iritis (inflammation of the iris) unresponsive to IDU alone and requiring steroid therapy.

The studies were reported in the Archives of Ophthalmology.

DISORDERS OF HEARING

HEARING CONSERVATION CRITERIA PROPOSED FOR CONTINUOUS NOISE

Many men and women in industry today are exposed to continuous, steady noise for long periods of time, and as a result, suffer hearing loss. NINDB grantees, after intensive research, have now arrived at specific hearing conservation criteria that will help prevent such deafness. In this study, the authors used as their measure of auditory impairment, the inability "to hear and understand everyday speech under everyday conditions."

The investigators have grouped noise exposure into three types: (1) steady continuous noise for 5 hours or more a day, 5 days a week, for many years: (2) steady continuous noise for less than 5 hours a day, 5 days a week, for many years: (3) steady noise that is intermittently heard during the day for 5 days a week, for many years. Separate hearing conservation criteria are proposed for each group, and curves are presented based on the calculations by which the criteria were determined.

The data also illustrate these important facts: The maximum change in hearing ability due to noise exposure occurs within 10 to 12 years, regardless of the exposure level. The ability to hear continues to decrease after 10 years, but the shift parallels the average loss in hearing that comes with increasing age.

This study was conducted by NINDB grantees Aram Glorig, M.D. (Subcommittee on Noise Research Center), W. Dixon Ward, Ph. D., and James Nixon, A.B., of Los Angeles, and reported in Archives of Otolaryngology.

TOXIC EFFECTS OF KANAMYCIN ON HUMAN EAR

NINDB grantees have been able to pinpoint pathologic changes in the human ear caused by a potent antibiotic drug, kanamycin. The toxic agents of the drug destroy portions of the auditory sense organ (organ of Corti) and its hair cells (elongated cells with hair like processes), which respond to sound. These results confirm previous studies of the effects of this drug in animals.

Kanamycin is effective in treating staphylococcus and other severe infections that resist milder antibiotics. However, it is recommended only as a possible, lifesaving measure because of its known toxicity to the ear, particularly in patients with impaired kidney function.

This study was conducted by Dr. Jaime T. Benitez, of Henry Ford Hospital in Detroit; Dr. Harold F. Schuknecht, formerly of Henry Ford Hospital, now of Massachusetts Eye & Ear Infirmary, Boston; and Capt. James H. Brandenburg, Medical Corps, U.S. Army, of Brooke Army Medical Center, Fort Sam Houston, Tex. The work is reported in Archives of Otolaryngology.

STREPTOMYCIN'S TOXIC EFFECTS LIMITED TO INNER EAR

NINDB grantees have shown conclusively that toxic effects of two antibiotics—streptomycin sulfate and dihydrostreptomycin—are limited to the inner ear and do not involve the brain stem.

In animal studies, both drugs destroyed the end organs in the vestibular portion of the inner ear, particularly the cristae (sense organs of the semicircular canal) with relative sparing of the maculae (sense organs of the vestibular portion of the bony labyrinth).

Dihydrostreptomycin caused delay, permanent hearing loss, occurring from several weeks to several months after the drug was administered. Streptomycin, however, was less toxic to the auditory system.

In this study, 27 healthy adult cats were divided into 5 groups. One group received toxic doses of streptomycin sulfate; the second group, dihydrostreptomycin. Both of these groups were tested for auditory and vestibular function during a 12- to 20-month followup.

A third group, which also received toxic doses of streptomycin sulfate, was examined for immediate pathological effects. In a fourth group, vitamin A and streptomycin sulfate were administered to determine the possible protective effects of the vitamin against the antibiotic. No protection was noted. The fifth group consisted of control animals.

Dr. T. Manford McGee of Henry Ford Hospital, Detroit, conducted the auditory and vestibular function tests on cats, both before and after drug administration. Dr. J. Olszewski, of the University of Toronto, without knowledge of the results of these tests, conducted histological examinations of the central nervous system of these animals.

The site of the toxic effects of the drugs is believed to be the same in humans, according to Dr. Harold F. Schuknecht, well-known otolaryngologist, who bases this opinion on his clinical experience with streptomycin ototoxicity in treating Meniere's disease.

This study is described in detail in Archives of Otolaryngology.

NINDB GRANTEES EXPLORE BASIS FOR HEREDITARY DEAFNESS IN DALMATIANS

NINDB grantees at Johns Hopkins University, studying hereditary deafness in the Dalmatian dog, found degenerative changes in parts of the inner ear but not in the brain or brain stem. These findings differ from those of a number of previous investigators, who reported that brain degeneration also occurred.

The hereditary deafness that is found in Dalmatians and other dappled dogs is paralleled in many by the congenital deafness which accompanies the Waardenburg syndrome. This disorder is characterized by a white forelock and eye mal-

formation. Both types of deafness are inherited and associated with a pigmentation defect.

Using deaf Dalmatian puppies and a normal one as control, the grantees correlated anatomical and electrophysiological findings. The abnormalities noted were collapse of the cochlear duct, degeneration of the hair cells of the auditory sense organ (organ of Corti), and collapse of the saccule, or sac connected to the cochlear duct. No electrical response to sound, either pure tones or click, was recorded at the round window membrane. The spiral ganglion cells, cochlear nerve, and central auditory system, however, were normal.

Since brain degeneration described in older animals did not occur in these puppies, the investigators suggest that the neural degeneration may progress with age.

Previous clinical studies of a child with deafness associated with the Waardenburg syndrome revealed degeneration of the hair cells of the organ of Corti and the spiral ganglion cells, but the brain and brain stem were intact, as in the present study of dogs.

The study was made by Dr. R. J. Ruben, Department of Otolaryngology, Johns Hopkins University School of Medicine, Baltimore, Md., and Dr. W. R. Hudson, now of Durham, N.C. Their work is reported in *Archives of Otolaryngology*.

FURTHER STUDIES TO UTILIZE SKIN AS COMMUNICATION CHANNEL REPORTED

A practical system for utilizing the skin as a communication channel, through the use of pain-free electric pulses, may soon be possible. Such a communication system could be of great benefit to the deaf-blind, in particular, and of practical use to the aviator, the frogman, and others.

The present study deals with the psychophysical approach to determine the boundaries between pain and painless pulses—problems of intensity, polarity, pulse duration and interval, and local skin areas being stimulated. Also, the problem of coding is considered, and a system for alpha-numeric coding is suggested.

Dr. B. von Haller Gilmer, of the Department of Psychology at Carnegie Institute of Technology, conducted this study, supported in part by a grant from the National Institute of Neurological Diseases and Blindness. His work is reported in the *Journal of Psychology*.

Dr. Gilmer's studies indicated that the palms of the hands and the soles of the feet are the most reliable areas to stimulate. Even after several hours' testing, the palms showed no irritation or decrease of pulse perception. Of the 200 subjects tested, none failed to perceive the pulse sensations, so there would probably be no problem of "skin deafness."

A pulse duration of 10 milliseconds was found to be optimum for the system: this duration is easily discriminated and does not increase the time required for communication. Pulse frequencies below eight pulses per second caused no unpleasant sensations, and pain threshold varied more than pulse threshold. Three levels of intensity and two levels of duration could be distinguished. Dr. Gilmer suggested that by using the different levels of intensity and duration and three loci on each palm, it might be possible to devise a code of 36 symbols, which would allow for 26 letters and 10 digits.

Further research in information processing, language structure analysis, and neural coding is essential for the development of cutaneous electropulse communication.

HIGHER CEREBRAL FUNCTION

SUBCORTICAL BRAIN AREA LINKED TO DISCRIMINATIVE CAPACITY

The role of a subcortical brain center called the subthalamus has been clarified, showing its relation to judgment or the discriminatory process. NINDB grantees demonstrated in cats that damage to the subthalamic area profoundly impaired discriminative capacity but did not affect motor response.

In addition, the grantees determined that the rhythmic, slow brain waves in the hippocampus (a part of the olfactory cortex) and in the subthalamic and related areas during performance tests are normal and signify discriminatory behavior. When discriminative capacity was impaired by damage to the subthalamus, the wave pattern disappeared, but when discriminative capacity was restored, the slow-wave pattern reappeared.

This study, supported in part by NINDB, was made by Dr. W. R. Adey, D. O. Walter, and D. F. Lindsley, of the University of California's Brain Research Institute and the Veterans' Administration Hospitals at Long Beach and Los Angeles, and reported in Archives of Neurology.

THURSDAY, MARCH 14, 1963.

GRANTS FOR CONSTRUCTION OF HEALTH RESEARCH FACILITIES

WITNESSES

DR. FREDERICK L. STONE, CHIEF, DIVISION OF RESEARCH FACILITIES AND RESOURCES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

GERALD SPARER, EXECUTIVE OFFICER, DIVISION OF RESEARCH FACILITIES AND RESOURCES

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

HARRY L. DORAN, CHIEF FINANCE OFFICER

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Program and financing

[In thousands of dollars]

	1962 actual	1963 estimate	1964 estimate
Program by activities: Grants for construction and equipment (costs—obligations) (object class 41).....	30,011	50,005	50,000
Financing:			
Unobligated balance brought forward (—).....	—16	—5	-----
Unobligated balance carried forward.....	5	-----	-----
New obligational authority (appropriation).....	30,000	50,000	50,000

GENERAL STATEMENT

Mr. FOGARTY. Dr. Stone, we will be pleased to hear from you on grants for construction of health research facilities.

Dr. STONE. The amount of \$50 million is requested for 1964 to support the program of Federal assistance in the construction and/or equipping of facilities for research in sciences related to health. In accordance with the requirements of title VII of the Public Health Service Act, as amended, grants awarded under this program are made on a matching basis, with the Federal share not exceeding 50 percent.

During the past 7 years, the Congress has made appropriations of \$230 million for this program. There has been a total of 1,039 grants to 369 institutions in 49 States, the District of Columbia, and Puerto Rico in an amount of \$229,977,555. There continues to be an orderly sequence of completion, occupancy, and utilization of new and remodeled research facilities. As of December 31, 1962, there was a total of 431 completed projects. These facilities represent a Federal investment of \$71,305,841, a 40-percent increase over the amount reported a year ago. Supplementary grants for movable equipment in these research facilities have not been included in this total.

Additional new facilities have been authorized. About 230 are under contract and some of these are nearing completion. There are 149 projects for which contract commitments have yet to be made.

Within the limits of available funds, the program has been extremely effective in meeting the needs for construction of facilities used for research programs in the sciences related to health.

During the 7 years of the health research facilities program, it has established a solid foundation of policies and procedures while maintaining the flexibility essential in a dynamic scientific community where rapid developments on a vast scale constantly create new types of needs.

That is a summation of my prepared statement.

Mr. FOGARTY. Thank you, Doctor. We will place your full statement in the record.

(The statement follows:)

Mr. Chairman and members of the committee, the amount of \$50 million is requested for 1964. This program provides Federal assistance in the construction and/or equipping of facilities for research in the sciences related to health. As such, it has become one of the strong resource programs through which the NIH is able to provide, on an institution-wide basis, assistance in developing those facilities which our universities and medical schools require to conduct effective research programs in the health sciences.

The program was authorized under Public Law 84-835, which added title VII to the Public Health Service Act. This title was extended for an additional 3-year period in August 1958 (Public Law 85-777), for a 1-year period in October 1961 (Public Law 87-395), and most recently for 3 additional years in October 1962 (Public Law 87-838). The extension in 1961 provided for an increase in the authorization from \$30 to \$50 million, together with modifications in the language. The principal change was to broaden the term "research facilities" to include research and related purposes, including research training.

In accordance with the requirements of title VII, grants awarded in this program are made on a matching basis, with the Federal share not exceeding 50 percent. To be eligible for support, an institution must be either a non-Federal public or a nonprofit private organization, which is competent to conduct the type of health-related research for which the facility has been designed, and which agrees to continue to do so for at least a 10-year period. Grants are awarded by the Surgeon General only after favorable recommendation by the National Advisory Council on Health Research Facilities.

During the past 7 years the Congress has made appropriations of \$230 million toward the construction costs of research facilities supported under this program.

PROGRAM DEVELOPMENTS

Within the limits of available funds, the program has been extremely effective in meeting the needs for construction of facilities used for research programs in the sciences related to health.

Although there has been a continuing demand for these funds ever since the program was initiated in 1956, as represented by the more than 1,400 applications that have been received to date, more recently there has developed an additional type of need—namely, a requirement that the NIH concentrate on early, effective implementation of construction programs calculated to serve the research and research training program needs of its categorical institutes and to make possible broad institutional programs, often of a developmental nature, serving markedly to increase research capability in newly emergent fields of scientific endeavor.

Although the program during the past 7 years has been more responsive to the research facilities needs of individual institutions, and more particularly to their specific needs at a departmental level, it also has served to meet generalized needs for additional research facilities in the areas of cardiovascular disease, cancer, metabolic disorders, mental health, and the like. This may be shown by a comparison of the awards to date listed on an institutional basis with the same awards listed on a categorical basis presented herein later on.

There has been a total of 1,039 grants to 369 institutions in 49 States, the District of Columbia, and Puerto Rico in an amount of \$229,977,555 during the past 7 years. On an institutional basis, these have been distributed as follows: research facilities in medical schools, \$117,588,467; in dental schools \$2,953,415; in schools of osteopathy \$5,469; in schools of public health, \$6,231,978. Research facilities in health-related areas of other schools, such as pharmacy, veterinary medicine, chemistry, and the biological sciences, \$55,739,123; and research facilities to other public and private institutions (chiefly hospitals) engaged in health-related research, \$47,459,103. Of these funds, 46 percent has been allocated to non-Federal public institutions and 54 percent to private nonprofit institutions.

From the standpoint of categorical areas of research for which these funds have provided facilities, an estimated breakdown is as follows: cardiovascular research facilities, \$3 million; cancer research facilities, \$7 million; facilities for research in basic medical sciences, \$185.5 million; facilities for research in mental health \$12.8 million; facilities for research in metabolic disturbances \$5 million; facilities for research in dental diseases, \$7.9 million; facilities for research in communicable and environmental diseases, \$6.2 million; facilities for research in neurological diseases, \$3 million. It must be pointed out that, since many of these facilities were established to strengthen general, institutional research programs, a breakdown of usage among categorical fields had to be estimated.

During the 7 years of the health research facilities program, it has established a solid foundation of policies and procedures while maintaining the flexibility essential in a dynamic scientific community where rapid developments on a vast scale constantly create new types of needs.

CONSTRUCTION PROGRESS

As might be expected of the program now in its seventh year of operation, there continues to be an orderly sequence of completion, occupancy, and utilization of new and remodeled research facilities. As of December 31, 1962, there was a total of 431 completed projects. These facilities represent a Federal investment of \$71,305,841, a 40-percent increase over the amount reported a year ago. Supplementary grants for movable equipment in these research facilities have not been included in this total.

Additional new facilities are in progress, with some 230 under contract, some of which are nearing completion, and 149 projects for which the final contract commitments have yet to be made.

PROGRAM DIRECTORS

Previous reference has been made in this report to the introduction of new factors which are certain to influence the program during the next several years. The Division of Research Facilities and Resources has extensive responsibilities with respect to providing facilities and broad support to health-related research institutions for those types of resources which strengthen the entire institution in its ability to conduct at a high level of excellence, modern biomedical research. If the Division is to be effective in serving this primary mission, the coordinated employment of title VII funds must be most selective in order to be most productive. Basic facilities for child health research centers, for general clinical research centers, for computer centers, for animal resource centers, and for specialized centers for the management of health research data and information are among the needs which must be met through the title VII program. It is anticipated that support will be provided for facilities to house research and related activities in the important areas of environmental health, mental health, and cancer chemotherapy, and in other emergent areas.

CURRENT STATUS

Against the amount proposed for 1964, there are the following estimated requirements, as of December 31, 1962:

	Funds requested	Anticipated approvals
1. Approved projects recommended by Council and awaiting payment.....	\$77,557,510	\$53,476,469
2. (a) Pending: new and deferred applications awaiting Council action (46)....	25,058,047	
2. (b). Anticipated approvals, based on 65 percent approval rate.....		16,287,730
3. Intentions to submit applications (90).....	30,342,893	
Anticipated approvals, based on 30 percent combined submission and approval rate.....		9,102,868
Total.....	132,958,450	78,867,067

This is the known demand, insofar as it can be documented by approved projects, pending applications, and formal intentions on file. This table does not include institutions which have declared their intention to submit applications but which could not provide construction costs estimates at this time.

APPLICATION BACKLOG

Mr. FOGARTY. The appropriation for 1963 is \$50 million and the request for 1964 is the same. This is the maximum authorized by law. What is the backlog in applications for this at the present time?

Dr. STONE. At the present moment it is about \$53 million of scientifically approved but unpaid applications.

Mr. FOGARTY. Does that mean you would not even be able to fund the approved projects already received?

Dr. STONE. Our 1963 appropriation has already been awarded completely. The \$53 million to which I referred will be approved applications not funded this year and will be funded from the 1964 appropriations.

Mr. FOGARTY. It looks to me like you are getting further behind all the time. We will put pages 187 and 188 of the justifications in the record, which explains this particular request.

(The pages follow:)

Grant for construction of health research facilities

1963 estimate.....	\$50,005,060
1964 estimate.....	50,000,000
Increase or decrease.....	-5,060

The Health Research Facilities Act of 1956, as amended, authorizes \$50 million annually through 1966.

Total appropriations of \$230 million have been made by the Congress through 1963.

Since the inception of the program 1,461 applications have been received requesting a total of \$447,294,073.

Upon the recommendation of the National Advisory Council on Health Research Facilities, the Surgeon General has thus far approved 1,039 grants, totaling \$229,977,755, to 368 institutions in 49 States, the District of Columbia, and Puerto Rico. One hundred and sixty-four applications, recommended by the National Advisory Council and awaiting final approval by the Surgeon General, total \$53,476,469.

The following breakdown indicates the kinds of health research facilities that are being constructed with the assistance of grants from this program:

Medical schools-----	\$117,588,467
Dental schools-----	2,953,415
Schools of Public Health-----	6,231,978
Other health-related schools ¹ -----	55,744,592
Institutions other than health-related schools ² -----	47,459,103
Total-----	229,977,555

¹ Includes schools of veterinary medicine, pharmacy, chemistry, and biological sciences.

² State, county, and municipal health agencies as well as hospitals and independent research institutions.

Grants made to eligible institutions for the construction and equipping of health-related research facilities range from support for such space in small nonprofit hospitals and foundations to support for all research areas in large medical centers. Specific examples are the following:

Children's Hospital, Birmingham, Ala.: Completion of research laboratories and equipment-----	\$27,100
Brown University, Providence, R.I.: Laboratories for research in psychology and equipment-----	105,686
Mayo Association, Rochester, Minn.: Renovation and expansion of medical science building-----	158,746
Portland State College, Portland.: Environmental public health research facilities-----	389,280
Michigan State University, East Lansing, Mich.: Biochemistry and biomedical research buildings-----	2,000,000

Against the amount proposed for 1964 there are the following estimated requirements:

Balance of recommended grants-----	\$53,476,469
Pending applications for future meetings-----	25,058,047
Intentions to file applications on record-----	30,342,893
Total-----	108,877,409

Other intentions to file are on record, but furnish no estimated amount of the proposed application.

The Surgeon General's Seventh Annual Report on Health Research Facilities Construction will be available prior to hearings of the Congressional Appropriations Subcommittees.

RECOMMENDATIONS OF ADMINISTRATION'S HEALTH PROGRAM

Mr. FOGARTY. What recommendations are included in the administration's health program that relate to this program?

You can supply that for the record.

(The recommendations follow:)

Two major measures encompassed within the administration's health program for fiscal year 1964, and which are now encompassed in legislation pending before the Congress, will have effects upon the administration and conduct of the health research facilities construction program now carried out by the National Institutes of Health under title VII of the Public Health Service Act:

(1) H.R. 12, the Health Professions Educational Assistance Act of 1963, as introduced into the Congress, contains several amendments to title VII.

(2) H.R. 3689, a bill to assist States in combating mental retardation, authorizes, through amendment to title VII, \$30 million to be expended over a 5-year period in the form of matching grants for the construction of centers for research in mental retardation.

The provisions of H.R. 12 that are pertinent to the health research facilities construction program are as follows:

(1) Section 711 would be added to title VII of the Public Health Service Act authorizing the Surgeon General to provide assistance to applicants in designing and planning the construction of facilities for the conduct of health-related research.

(2) H.R. 12 also provides for the addition of a section 712 to title VII of the Public Health Service Act which would authorize the Surgeon General to construct, or make arrangements for constructing, facilities for the conduct of health-related research where the facilities would be of particular value or significance for the Nation or a region thereof and pay for such construction in part or in total.

However, the version of H.R. 12 recently reported by the House Interstate and Foreign Commerce Committee did not contain this proposed section 712. If, however, the provisions of section 712 were to be incorporated in this legislation and enacted, this would significantly enlarge the ability of the National Institutes of Health to develop health research facilities required for national or regional purposes.

(3) Title VII of the Public Health Service Act would also be amended to require that prevailing wage rates in accordance with the Davis-Bacon Act be paid to laborers and mechanics in the performance of work on the construction of facilities supported through the health research facilities construction program.

H.R. 3689 would add a part B to title VII of the Public Health Service Act authorizing \$30 million to be expended over a 5-year period for the construction of centers for research on mental retardation and related aspects of human development through matching grants.

COMPLIANCE WITH GAO REPORT

Mr. FOGARTY. With what criticisms included in the recent GAO report do you agree and with which do you disagree? What have you done as a result of this report?

Dr. STONE. We have actually taken steps to increase this staff in needed areas, specifically management, financial management, and we hope that our plans for the establishment of a section on architectural and engineering standards will be approved. The pieces of paper that are concerned with this request are on their way through channels to the proper echelons in the Service. The criticisms to which you refer were those which were made of the program 6 years ago. We feel that proper steps have been taken to see that the criticisms will not be merited in the future.

Mr. FOGARTY. There is no problem now?

Dr. STONE. The GAO is in the process, at the present time, of reviewing the steps we have taken; I can't speak for them officially, but unofficially we have had reason to believe that they are satisfied with the steps that we have already taken and that we are planning to take in the future.

Mr. FOGARTY. Thank you, Doctor.

Mr. Laird?

TRENDS IN FEDERAL SUPPORT OF RESEARCH AT COLLEGES AND UNIVERSITIES

Mr. LAIRD. I have no questions, but after our first day's hearing with Dr. Shannon, I asked him to get me some more information regarding trends in Federal support of research at colleges and universities, which he has done. I would like to place this additional information in the record, Mr. Chairman.

Mr. FOGARTY. We will enter it in the record at this point.

(The information follows:)

Total Federal support of research at colleges and universities has increased from \$295 million in 1952 to an estimated \$1,266 million in 1962. These dollar amounts include support provided for research performed in the university set-

ting proper, and the research performed at university-managed Federal contract research centers such as Los Alamos, Argonne, and the Jet Propulsion Laboratory. In the earlier year, research centers received almost half of all Federal support; in 1962 the proportion had declined to 44 percent.

The following table presents a summary by Federal agency of the support provided for research performed by universities both within the educational institution setting, and at the research centers.

From 1952 to 1962 all Federal agencies increased their support to educational institutions, but there have been significant shifts in the proportions of the total provided by individual agencies.

In 1952, the Defense Department provided more than 50 percent of all Federal funds going to educational institutions; the Atomic Energy Commission supplied more than one-third of the total. By 1962 the Defense Department and AEC together provided only 50 percent of the Federal funds (25 percent each). In 1962, National Institutes of Health research grants accounted for more than one-fifth of Federal support to educational institutions—as compared with one-twentieth in 1952. Last year, research programs of the National Aeronautics and Space Administration accounted for 14 percent of the total.

Support of the university-managed Federal contract research centers is primarily provided by the Defense Department, AEC, and NASA. In 1952, Defense Department programs accounted for about one-third of the total and AEC the remaining two-thirds. In 1962, AEC sponsored one-half of the research at these university-managed centers, NASA almost 30 percent, and the Defense Department the remaining one-fifth.

Significant shifts have also occurred over the past 10 years in the agency support of research performed in the university setting proper. In 1952, the Defense Department supplied 70 percent of these funds, NIH about 10 percent, and AEC and all other Federal agencies the remaining 20 percent. By 1962, the broad research programs of NIH, drawing largely upon the resources of our educational institutions, contributed two-fifths of Federal support; Defense Department funds have declined to less than 30 percent. Research grants of the National Science Foundation now amount to 12 percent of Federal funds for research in the university setting, a substantial increase from the 1 percent provided by that agency in 1952. AEC and all other Federal agencies combined continue to contribute about one-fifth of the funds for this purpose.

Federal support of research at educational institutions, 1952 and 1962

Agency	1952, educational institutions			1962, educational institutions		
	Total	Proper	Research centers	Total	Proper	Research centers
	<i>Millions</i>	<i>Millions</i>	<i>Millions</i>	<i>Millions</i>	<i>Millions</i>	<i>Millions</i>
Total.....	\$294.7	\$151.2	\$143.5	\$1,266.4	\$715.2	\$551.2
National Institutes of Health.....	14.4	14.4	-----	282.2	282.2	-----
National Science Foundation.....	1.0	1.0	-----	85.7	85.7	-----
Department of Defense.....	155.7	105.5	50.2	312.5	200.8	111.7
Other agencies.....	123.6	30.3	93.3	585.9	146.5	439.4
Atomic Energy Commission.....	105.3	13.4	91.9	334.8	50.9	283.8
National Aeronautics and Space Administration.....	-----	-----	-----	180.0	25.0	155.0
All other agencies.....	18.3	16.9	1.4	71.1	70.6	.6
Total.....	<i>Percent</i> 100	<i>Percent</i> 100	<i>Percent</i> 100	<i>Percent</i> 100	<i>Percent</i> 100	<i>Percent</i> 100
National Institutes of Health.....	5	9	-----	22	40	-----
National Science Foundation.....	(¹)	1	-----	7	12	-----
Department of Defense.....	53	70	35	25	28	20
Other agencies.....	42	20	65	46	20	80
Atomic Energy Commission.....	36	9	64	25	7	51
National Aeronautics and Space Administration.....	-----	-----	-----	14	3	28
All other agencies.....	6	11	1	7	10	(¹)

¹ Less than 0.5 percent.

NOTE.—Details will not add to totals because of rounding.

Source: Data for 1952, National Science Foundation, Federal Funds for Science I, and estimates by NIH. Data for 1962, National Science Foundation, statistics to be published in forthcoming Federal Funds for Science XI; data for NIH revised to reflect actual obligations.

AWARD OF PUBLIC WELFARE MEDAL OF THE NATIONAL ACADEMY OF
SCIENCES TO DR. SHANNON

MR. FOGARTY. This concludes our hearings on the 1964 budget for the National Institutes of Health, but before we adjourn I want to call attention to a high honor bestowed on Dr. Shannon since we closed our hearings last year. I will read the National Academy of Sciences press release of last April 24.

The Public Welfare Medal of the National Academy of Sciences will be presented to Dr. James A. Shannon, Director of the National Institutes of Health, the academy announced today. The presentation will be made by Dr. Detlev W. Bronk, president of the National Academy of Sciences, at the Academy's annual dinner to be held tonight (April 24) at the Statler-Hilton Hotel here. The occasion is part of the Academy's 99th annual meeting being held April 23-25 at the Academy Building. The Public Welfare Medal, awarded for "eminence in the application of science to the public welfare," is considered to be the most distinguished of the Academy medals.

Established in 1913 by Mrs. Helen Hartley Jenkins in honor of her father, Marcellus Hartley, the Public Welfare Medal is unique among the Academy medals in that it is awarded for outstanding achievement in the uses of science for human welfare rather than in the advancement of scientific knowledge in a particular discipline. In presenting this award, the Academy also gives further special recognition to its recipients—many of them not research scientists—in the form of certain privileges of Academy membership, including the right to present papers at meetings of the Academy.

Dr. Shannon, as Director of the National Institutes of Health, is responsible not only for research conducted in NIH laboratories and clinics but also for its support of medical and biological research and research training, and expansion of health-research facilities throughout the Nation. Under Dr. Shannon's leadership, support of these programs has increased from \$81 million in 1955 to more than \$775 million in the current fiscal year. NIH now supports almost 40 percent of the Nation's medical and biological research.

Dr. Shannon's World War II activities included broad responsibility for the development of antimalarial therapy for the Armed Forces. Since that time, in addition to his many other contributions to public health, he has served as the U.S. member of the Research Advisory Council of the World Health Organization and in various important capacities in the National Academy of Sciences—National Research Council's Division of Medical Sciences.

The last recipient of the Public Welfare Medal was Dr. Alan T. Waterman. Other recent recipients have included Lt. Gen. James H. Doolittle, Dr. Henry Allen Moe, Dr. Warren Weaver, Dr. James R. Killian, Jr., David E. Lilienthal, George Harrison Shull, Karl Taylor Compton, Vannevar Bush, and John D. Rockefeller, Jr.

I think this was a well-deserved honor, Dr. Shannon. I am sure all of the members of this committee were happy to see you receive this recognition for your outstanding service.

DR. SHANNON. Thank you very much, Mr. Chairman.

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